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OFFICE OF PETITIONS

Patent Department
Boehringer Ingelheim Corp.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368
Tel: (203) 798-5285
Date: 03/15/2004

"EXPRESS MAIL" LABEL NO.:
EV 364730221 US
DEPOSIT DATE: March 15, 2004

1. Application for Extension of Patent Term Under 35 USC §156, with Exhibits A-I (In Triplicate)
2. Fee Transmittal for FY 2004 (In Triplicate)
3. Express Mail Certificate
4. Return Post Card

I HEREBY CERTIFY THAT THE ABOVE PAPERS AND FEE ARE BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO:

Commissioner for Patents
Mail Stop Patent Extension
P. O. Box 1450
Alexandria, VA 22313-1450

By: Michael P. Morris

Michael P. Morris
Reg. No. 34.513

PTO/SB/17 (10-03)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 1,120.00

Complete if Known	
Application Number	US Pat. 5,610,163
Filing Date	Issued: 03/11/1997
First Named Inventor	Banholzer, et al
Examiner Name	
Art Unit	
Attorney Docket No.	US Pat. 5,610,163 PTE

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☑ Deposit Account:

Deposit Account Number: 02-2955

Deposit Account Name: 02-2955

The Director is authorized to: *(check all that apply)*

☑ Charge fee(s) indicated below ☑ Credit any overpayments

☑ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below	Fee Paid
Total Claims	-20** =	X	18.00	=
Independent Claims	- 3** =	X	86.00	=
Multiple Dependent			290.00	=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

***or number previously paid, if greater; For Reissues, see above*

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) Appln. Pat. Term Ext. 37 CFR 1.20(j) 1,120.00

*Reduced by Basic Filing Fee Paid **SUBTOTAL (3)** ($) 1,120.00

SUBMITTED BY				(Complete *(if applicable)*)	
Name (Print/Type)	Michael P. Morris	*Registration No. (Attorney/Agent)*	34,513	*Telephone*	203/798-5285
Signature	Michael P. Morris			*Date*	03/15/2004

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/17 (10-03)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Attorney Docket No.	US Pat. 5,610,163 PTE

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**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

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Other fee (specify) Appln. Pat. Term Ext. 37 CFR 1.20(j)					1,120.00

*Reduced by Basic Filing Fee Paid **SUBTOTAL (3)** ($) 1,120.00

SUBMITTED BY				(Complete *(if applicable)*)	
Name (Print/Type)	Michael P. Morris	*Registration No. (Attorney/Agent)*	34,513	*Telephone*	203/798-5285
Signature	Michael P. Morris			*Date*	03/15/2004

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

This collection of information is required by 37 CFR 1.17 and 1.27. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re	:	U. S. Patent 5,610,163
Issued	:	March 11, 1997
Inventors	:	Banholzer, et al
For	:	Esters of Thienyl Carboxylic Acids And Amino Alcohols And Their Quaternization Products

Mail Stop Patent Extension
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Sir:

Boehringer Ingelheim KG, a corporation of the Federal Republic of Germany (hereinafter called "the Applicant") and the owner of record of U. S. Patent No. 5,610,163 hereby applies for an extension of the term of U. S. Patent No. 5,610,163 pursuant to the provisions of 35 U.S.C. § 156 and 37 C. F. R. §§ 1.710 – 1.791.

The Applicant seeks extension of the term of U. S. Patent No. 5,610,163 for a period of 1,421 days, so that the expiration date of the patent would be changed from 11 March 2014 to 30 January 2018.

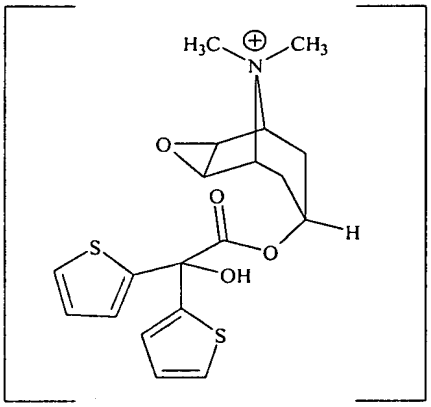
DETAILED DESCRIPTION OF BASIS FOR THE APPLICATION

Provided below is the information required by 37 C.F.R. § 1.740(a).

1. A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics

The approved product is tiotropium bromide monohydrate.

Tiotropium bromide monohydrate is the drug substance present in, and thus the active ingredient of, the new drug Spiriva® HandiHaler® (tiotropium bromide inhalation powder).[1] It has the following structural formula:



Tiotropium bromide is the United States Adopted Name (USAN) for the active ingredient.[2]

[1] See the text of Package Insert, which is attached hereto as Exhibit A.
[2] In accordance with convention, the USAN does not take into consideration the hydration state of the active ingredient.

Ignoring the state of hydration, the active ingredient may also be identified by the following chemical names:

(1α,2β,4β,5α,7β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane-bromide;

3-Oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane, 7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-,bromide, (1α,2β,4β,5α,7β)-; and

6β,7β-epoxy-3β-hydroxy-8-methyl-1αH,5αH-tropanium bromide, di-2-thienyl-glycolate.

2. A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred

The approved product was the subject of regulatory review under the provisions of Section 505 of the Federal Food, Drug & Cosmetic Act, as amended (21 U.S.C. § 355).

3. An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred

The product received permission for commercial marketing or use under the provisions of Section 505 of the Federal Food, Drug & Cosmetic Act (21 U.S. C. § 355) on 30 January 2004, the date New Drug Application (NDA) No. 21-395 was approved by the United States Food and Drug Administration.

4. An identification of each active ingredient in the drug product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug & Cosmetic Act, the Public Health Service Act, or the Virus-Serum Toxin Act

The sole active ingredient in the new drug product Spiriva® HandiHaler® (tiotropium bromide inhalation powder) is tiotropium bromide monohydrate.

The active moiety or component of the active ingredient is tiotropium. Tioptropium is the positively charged moiety in the structural formula for tiotropium bromide provided above.

It is the Applicant's information and belief that neither tiotropium bromide (regardless of hydration state) nor tiotropium (regardless of hydration state or counter-anion) have previously been approved for commercial marketing or use under the Federal Food, Drug & Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

5. A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted

This application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f). Such sixty day period will expire on 30 March 2004.

6. An identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration

The patent for which an extension is being sought is U. S. Patent No. 5,610,163. It issued on 11 March 1997. Absent any extension which may be granted as a result of the present application, it will expire on 11 March 2014.[3] The inventors named in the patent are Rolf Banholzer, of Ingelheim am Rhein, Rudolf Bauer, of Wiesbaden, and Richard Reichel, of Ingelheim am Rhein, all of the Federal Republic of Germany.

7. A copy of the patent for which extension is being sought, including the entire specification (including claims) and drawings

A copy of U. S. Patent No. 5,610,163, the patent for which extension is being sought, including the entire specification (including claims) and drawings is attached hereto as Exhibit B.

[3] The term of U. S. Patent No. 5,610,163 was determined in the following manner: It issued on 11 March 1997 and results from an application (Ser. No. 405,111) filed on 16 March 1995. Thus, its term is to be determined in accordance with 35 U.S.C. §154(c)(1), which states, "The term of a patent that is in force on or that results from an application filed before the date that is 6 months after the date of the enactment of the Uruguay Round Agreements Act shall be the greater of the 20-year term as provided in subsection (a), or 17 years from grant, subject to any terminal disclaimers." (The Uruguay Round Agreements Act was enacted on 8 December 1994.) Further, U. S. Patent No. 5,610,163 contains a specific reference to several earlier filed applications under 35 USC §120, the earliest of which is Ser. No. 838,724, filed 13 March 1992. Thus, its term is the greater of 20 years from the earliest filed application under 35 USC 120 (13 March 1992) as provided by 35 U.S.C. § 154(a), or 17 years from grant (11 March 1997). The term calculated as 17 years from grant yields the greater result. Accordingly, the patent will expire on 11 March 2014.

8. A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent

Copies of the three (3) Certificates of Correction issued for U. S. Patent No. 5,610,163 are attached hereto as Exhibit C.

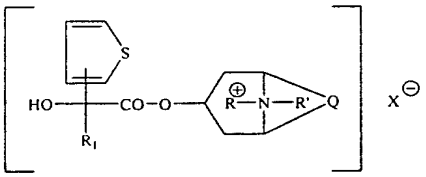
Copies of the maintenance fee statement showing the status of payment of the first maintenance fee as PAID is attached hereto as Exhibit D.

9. A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or method of using or manufacturing the approved product

U. S. Patent No. 5,610,163 claims the approved product.

The applicable patent claims which read on the approved product are Claims 1 – 5, 7, 11 and 14. The text of these claims, as amended by the Certificates of Correction dated 4 July 2000 and 3 December 2002, is provided by Exhibit E.

Claim 1 reads on the approved product because the approved product, tiotropium bromide (regardless of its state of hydration), is a compound of the formula



wherein

Q is a group of the formula

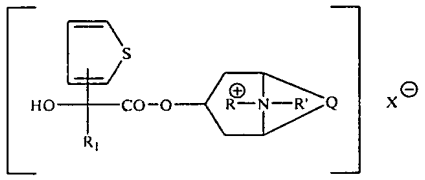

;

R and R' are each methyl (which is a C_1-C_4-alkyl);

R_1 is thienyl; and,

X^- is a bromide ion (which is a physiologically acceptable anion).

Claims 2, 3 and 4 read on the approved product because tiotropium bromide (regardless of its state of hydration) is a compound of the formula



wherein

R is CH_3;

R' is CH_3;

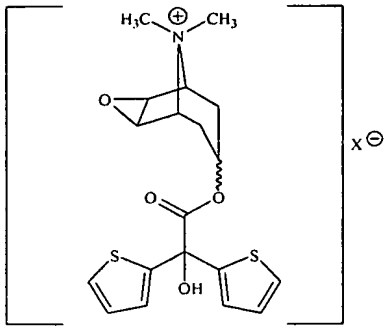
R_1 is thienyl;

Q is a group of the formula


; and,

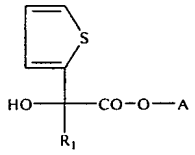
X^- is a bromide ion (which is a physiologically acceptable anion).

Claim 5 reads on the approved product because tiotropium bromide (regardless of its state of hydration) is a compound of the formula



wherein X- is a bromide ion (which is a physiologically acceptable anion).

Claim 7 reads on the approved product because tiotropium bromide (regardless of its state of hydration) is a compound of the formula



wherein R_1 is 2-thienyl and A is 3α-(6β, 7β-epoxy)-tropanyl methobromide.

Claim 11 reads on a method of using the approved product because it is directed to a method for treating chronic obstructive bronchitis which comprises administering, by inhalation, to a subject suffering from the same, a therapeutic amount of a compound in accordance with claims 1, 2, 3, 4 or 7. It has already been established above that claims 1, 2, 3, 4 and 7 read on the approved product, tiotropium bromide (regardless of hydration state). Further, the approved indication for the new drug Spiriva® HandiHaler® (tiotropium bromide inhalation powder) is "the long-term, once daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema." The use recited in claim 11 may fairly be said to correspond to the approved indication for the new drug, of which tiotropium bromide is the sole active ingredient.

Claim 14 reads on the approved product because it is directed to a pharmaceutical composition, for administration by inhalation, suitable for the treatment of chronic obstructive bronchitis or slight to moderately severe asthma, which comprises a compound in accordance with claims 1, 2, 3, 4, or 7. It has already been established that the sole active ingredient of the approved new drug is a compound in accordance with claims 1, 2, 3, 4 and 7. The new drug is administered by inhalation and is, as established above, suitable for the treatment of COPD, including chronic bronchitis.

10. A statement beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(*Only subparagraph (i) is applicable. Subparaph (i) reads as set forth below.*)

(i) For a patent claiming a human drug, antibiotic, or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;

(B) The date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and

(C) The date on which the NDA was approved or the Product License issued.

The required statement appears in Exhibit F.

11. A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities

The required brief description appears in Exhibit G.

12. A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined

The required statement appears in Exhibit H.

13. A statement that the applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought

The undersigned attorney for Applicant acknowledges, on behalf of the Applicant, a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information that is material to the determination of entitlement to the extension sought.

14. The prescribed fee for receiving and acting upon the application for extension

The prescribed fee of $1,120 pursuant to 37 C.F.R. § 1.20(j) may be charged to Deposit Account No. 02-2955. In addition, the Commissioner is hereby authorized to charge any additional fees necessary, or to refund any overpayment, to Deposit Account 02-2955. A duplicate copy of this Fee Authorization paper is also submitted herewith.

15. The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed

Direct all correspondence relating to this application to:

Michael P. Morris
Boehringer Ingelheim Corporation
900 Ridgebury Road, P. O. Box 368
Ridgefield, CT 06877-0368

Phone No. (203) 798-5285
Fax No. (203) 798-4408
E-mail: mmorris2@rdg.boehringer-ingelheim.com

This application is accompanied by two additional copies of such application (for a total of three copies).

Pursuant to 37 C.F.R. § 1.730(b)(2), this application is signed by a registered practitioner on behalf of the patent owner. Proof that this practitioner is authorized to act on behalf of the patent owner is supplied by the APPOINTMENT OF ATTORNEY FOR PURPOSES OF PATENT TERM EXTENSION UNDER 35 U.S.C. §156 that is attached hereto as Exhibit I.

BOEHRINGER INGELHEIM KG

Date: March 15, 2004

By: Michael P. Morris
Michael P. Morris
Attorney for Applicant
Registration No. 34,513

EXHIBIT A

ATTENTION PHARMACISTS: Detach "Patient's Instructions for Use" and dispense with the product.

Boehringer Ingelheim

Spiriva® HandiHaler®

(tiotropium bromide inhalation powder)

For Oral Inhalation Only

Prescribing Information

DESCRIPTION

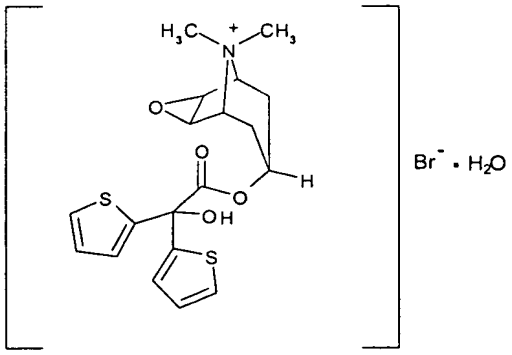
Spiriva HandiHaler consists of a capsule dosage form containing a dry powder formulation of Spiriva (tiotropium bromide) intended for oral inhalation only with the HandiHaler inhalation device.

Each light green, hard gelatin capsule contains 18 mcg tiotropium (equivalent to 22.5 mcg tiotropium bromide monohydrate) blended with lactose monohydrate as the carrier.

The dry powder formulation within the capsule is intended for oral inhalation only.

The active component of Spiriva is tiotropium. The drug substance, tiotropium bromide monohydrate, is an anticholinergic with specificity for muscarinic receptors. It is chemically described as (1α,2ß,4ß,5α,7ß)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane bromide monohydrate. It is a synthetic, non-chiral, quaternary ammonium compound. Tiotropium bromide is a white or yellowish white powder. It is sparingly soluble in water and soluble in methanol.

The structural formula is:



Tiotropium bromide (monohydrate) has a molecular mass of 490.4 and a molecular formula of $C_{19}H_{22}NO_4S_2Br \cdot H_2O$.

The HandiHaler is an inhalation device used to inhale the dry powder contained in the Spiriva capsule. The dry powder is delivered from the HandiHaler device at flow rates as low as 20 L/min. Under standardized *in vitro* testing, the HandiHaler device delivers a mean of 10.4 mcg tiotropium when tested at a flow rate of 39 L/min for 3.1 seconds (2L total). In a study of 26 adult patients with chronic obstructive pulmonary disease (COPD) and severely compromised lung function [mean FEV_1 1.02 L (range 0.45 to 2.24 L); 37.6% of predicted (range 16%-65%)], the median peak inspiratory flow (PIF) through the HandiHaler device was 30.0 L/min (range 20.4 to 45.6 L/min). The amount of drug delivered to the lungs will vary depending on patient factors such as inspiratory flow and peak inspiratory flow through the HandiHaler device, which may vary from patient to patient, and may vary with the exposure time of the capsule outside the blister pack.

For administration of Spiriva, a capsule is placed into the center chamber of the HandiHaler device. The capsule is pierced by pressing and releasing the button on the side of the inhalation device. The tiotropium formulation is dispersed into the air stream when the patient inhales through the mouthpiece. (See **Patient's Instructions For Use**)

CLINICAL PHARMACOLOGY

Mechanism of Action

Tiotropium is a long-acting, antimuscarinic agent, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors, M_1 to M_5. In the airways, it exhibits pharmacological effects through inhibition of M_3-receptors at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical *in vitro* as well as *in vivo* studies prevention of methacholine-induced bronchoconstriction effects were dose-dependent and lasted longer than 24 hours. The bronchodilation following inhalation of tiotropium is predominantly a site-specific effect.

Pharmacokinetics

Tiotropium is administered by dry powder inhalation. In common with other inhaled drugs, the majority of the delivered dose is deposited in the gastrointestinal tract and, to a lesser extent, in the lung, the intended organ. Many of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy.

Absorption:

Following dry powder inhalation by young healthy volunteers, the absolute bioavailability of 19.5% suggests that the fraction reaching the lung is highly bioavailable. It is expected from the chemical structure of the compound (quaternary ammonium compound) that tiotropium is poorly absorbed from the gastrointestinal tract. Food is not expected to influence the absorption of tiotropium for the same reason. Oral solutions of tiotropium have an absolute bioavailability of 2-3%. Maximum tiotropium plasma concentrations were observed five minutes after inhalation.

Distribution:

Tiotropium shows a volume of distribution of 32 L/kg indicating that the drug binds extensively to tissues. The drug is bound by 72% to plasma proteins. At steady state, peak tiotropium plasma levels in COPD patients were 17-19 pg/mL when measured 5 minutes after dry powder inhalation of an 18 mcg dose and decreased rapidly in a multi-compartmental manner. Steady-state trough plasma concentrations were 3-4 pg/mL. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium does not readily penetrate the blood-brain barrier.

Biotransformation:

The extent of biotransformation appears to be small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. Tiotropium, an ester, is nonenzymatically cleaved to the alcohol *N*-methylscopine and dithienylglycolic acid, neither of which bind to muscarinic receptors.

In vitro experiments with human liver microsomes and human hepatocytes suggest that a fraction of the administered dose (74% of an intravenous dose is excreted unchanged in the urine, leaving 25% for metabolism) is metabolized by cytochrome P450-dependent oxidation and subsequent glutathione conjugation to a variety of Phase II metabolites. This enzymatic pathway can be inhibited by CYP450 2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene. Thus, CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a small part of the administered dose. *In vitro* studies using human liver microsomes showed that tiotropium in supra-therapeutic concentrations does not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4.

Elimination:

The terminal elimination half-life of tiotropium is between 5 and 6 days following inhalation. Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers with an inter-individual variability of 22%. Intravenously administered tiotropium is mainly excreted unchanged in urine (74%). After dry powder inhalation, urinary excretion is 14% of the dose, the remainder being mainly non-absorbed drug in the gut which is eliminated via the feces. The renal clearance of tiotropium exceeds the creatinine clearance, indicating active secretion into the urine. After chronic once-daily inhalation by COPD patients, pharmacokinetic steady state was reached after 2-3 weeks with no accumulation thereafter.

Drug Interactions:

An interaction study with tiotropium (14.4 mcg intravenous infusion over 15 minutes) and cimetidine 400 mg three times daily or ranitidine 300 mg once daily was conducted. Concomitant administration of cimetidine with tiotropium resulted in a 20% increase in the AUC_{0-4h}, a 28% decrease in the renal clearance of tiotropium and no significant change in the C_{max} and amount excreted in urine over 96 hours. Co-administration of tiotropium with ranitidine did not affect the pharmacokinetics of tiotropium. Therefore, no clinically significant interaction occurred between tiotropium and cimetidine or ranitidine.

Electrophysiology:

In a multicenter, randomized, double-blind trial that enrolled 198 patients with COPD, the number of subjects with changes from baseline-corrected QT interval of 30-60 msec was higher in the Spiriva group as compared with placebo. This difference was apparent using both the Bazett (QTcB) [20 (20%) patients vs. 12 (12%) patients] and Fredericia (QTcF) [16 (16%) patients vs. 1 (1%) patient] corrections of QT for heart rate. No patients in either group had either QTcB or QTcF of >500 msec. Other clinical studies with Spiriva did not detect an effect of the drug on QTc intervals.

Special Populations:

Elderly Patients:

As expected for drugs predominantly excreted renally, advanced age was associated with a decrease of tiotropium renal clearance (326 mL/min in COPD patients <58 years to 163 mL/min in COPD patients >70 years), which may be explained by decreased renal function. Tiotropium excretion in urine after inhalation decreased from 14% (young healthy volunteers) to about 7% (COPD patients). Plasma concentrations were numerically increased with advancing age within COPD patients (43% increase in AUC_{0-4} after dry powder inhalation), which was not significant when considered in relation to inter- and intra-individual variability. (See **DOSAGE AND ADMINISTRATION SECTION**)

Hepatically-impaired Patients:

The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied. However, hepatic insufficiency is not expected to have relevant influence on tiotropium pharmacokinetics. Tiotropium is predominantly cleared by renal elimination (74% in young healthy volunteers) and by simple non-enzymatic ester cleavage to products that do not bind to muscarinic receptors. (See **DOSAGE AND ADMINISTRATION SECTION**)

Renally-impaired Patients:

Since tiotropium is predominantly renally excreted, renal impairment was associated with increased plasma drug concentrations and reduced drug clearance after both intravenous infusion and dry powder inhalation. Mild renal impairment (CrCl 50-80 mL/min), which is often seen in elderly patients, increased tiotropium plasma concentrations (39% increase in AUC_{0-4} after intravenous infusion). In COPD patients with moderate to severe renal impairment (CrCl <50 mL/min), the intravenous administration of tiotropium resulted in doubling of the plasma concentrations (82% increase in AUC_{0-4}), which was confirmed by

plasma concentrations after dry powder inhalation. (See **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS** Sections)

CLINICAL STUDIES

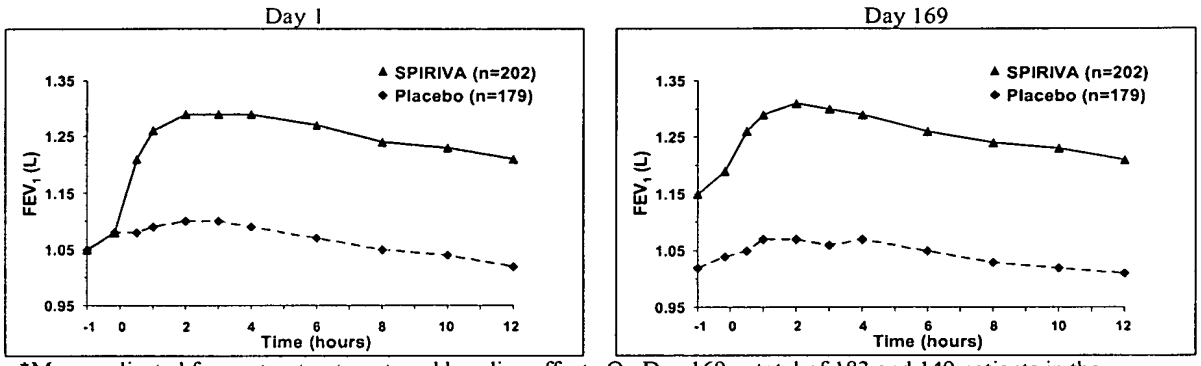
The Spiriva HandiHaler clinical development program consisted of six phase 3 studies in 2,663 patients with COPD (1,308 receiving Spiriva): two 1-year, placebo-controlled studies, two 6-month, placebo-controlled studies and two 1-year, ipratropium-controlled studies. These studies enrolled patients who had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking greater than 10 pack-years, had an FEV_1 less than or equal to 60 or 65% of predicted, and a ratio of FEV_1/FVC of less than or equal to 0.7.

In these studies, Spiriva, administered once-daily in the morning, provided improvement in lung function (forced expiratory volume in one second, FEV_1), with peak effect occurring within 3 hours following the first dose.

In the 1-year, placebo controlled trials, the mean improvement in FEV_1 at 30 minutes was 0.13 liters (13%) with a peak improvement of 0.24 liters (24%) relative to baseline after the first dose (day 1). Further improvements in FEV_1 and FVC were observed with pharmacodynamic steady state reached by day 8 with once-daily treatment. The mean peak improvement in FEV_1, relative to baseline, was 0.28 to 0.31 liters (28% to 31%), after 1 week (day 8) of once-daily treatment. Improvement of lung function was maintained for 24 hours after a single dose and consistently maintained over the 1-year treatment period with no evidence of tolerance.

In the two 6-month, placebo-controlled trials, serial spirometric evaluations were performed throughout daytime hours in Trial A (12 hours) and limited to 3 hours in Trial B. The serial FEV_1 values over 12 hours (Trial A) are displayed in Figure 1. These trials further support the improvement in pulmonary function (FEV_1) with Spiriva, which persisted over the spirometric observational period. Effectiveness was maintained for 24 hours after administration over the 6-month treatment period.

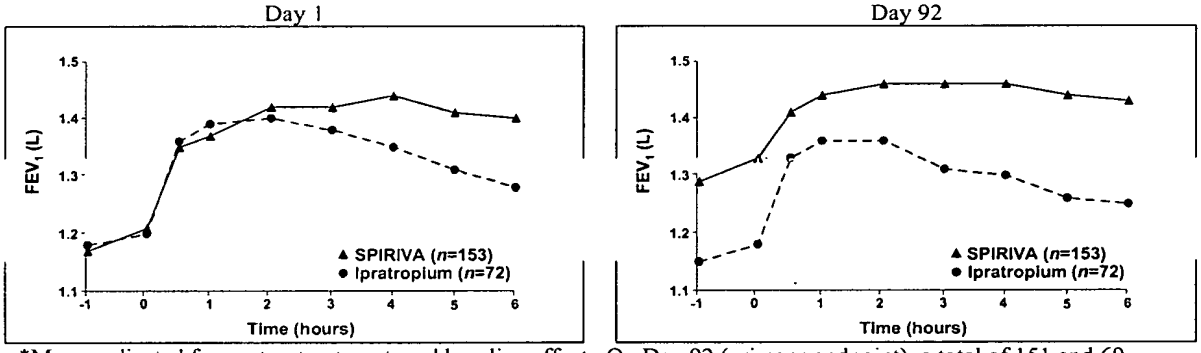
Figure 1: Mean FEV_1 Over Time (prior to and after administration of study drug) on Days 1 and 169 for Trial A (a Six-Month Placebo-Controlled Study)*



*Means adjusted for center, treatment, and baseline effect. On Day 169, a total of 183 and 149 patients in the Spiriva and placebo groups, respectively, completed the trial. The data for the remaining patients were imputed using last observation or least favorable observation carried forward.

Results of each of the one-year ipratropium-controlled trials were similar to the results of the one-year placebo-controlled trials. The results of one of these trials are shown in Figure 2.

Figure 2: Mean FEV_1 Over Time (0 to 6 hours postdose) on Days 1 and 92, respectively for one of the two Ipratropium-Controlled Studies*



*Means adjusted for center, treatment, and baseline effect. On Day 92 (primary endpoint), a total of 151 and 69 patients in the Spiriva and ipratropium groups, respectively, completed through three months of observation. The data for the remaining patients were imputed using last observation or least favorable observation carried forward.

A randomized, placebo-controlled clinical study in 105 patients with COPD demonstrated that bronchodilation was maintained throughout the 24-hour dosing interval in comparison to placebo, regardless of whether Spiriva was administered in the morning or in the evening.

Throughout each week of the one-year treatment period in the two placebo-controlled trials, patients taking Spiriva had a reduced requirement for the use of rescue short-acting $beta_2$-agonists. Reduction in the use of rescue short-acting $beta_2$-agonists, as compared to placebo, was demonstrated in one of the two 6-month studies.

INDICATIONS AND USAGE

Spiriva HandiHaler is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

CONTRAINDICATIONS

Spiriva HandiHaler is contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, including ipratropium, or to any component of this product.

WARNINGS

Spiriva HandiHaler is intended as a once-daily maintenance treatment for COPD and is not indicated for the initial treatment of acute episodes of bronchospasm, i.e., rescue therapy.

Immediate hypersensitivity reactions, including angioedema, may occur after administration of Spiriva. If such a reaction occurs, therapy with Spiriva should be stopped at once and alternative treatments should be considered.

Inhaled medicines, including Spiriva, may cause paradoxical bronchospasm. If this occurs, treatment with Spiriva should be stopped and other treatments considered.

PRECAUTIONS

General

As an anticholinergic drug, Spiriva may potentially worsen symptoms and signs associated with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction and should be used with caution in patients with any of these conditions.

As a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of ≤ 50 mL/min) treated with Spiriva should be monitored closely. (See **CLINICAL PHARMACOLOGY**, **Pharmacokinetics**, Special Populations: *Renally-impaired Patients*)

Information for Patients

It is important for patients to understand how to correctly administer Spiriva capsules using the HandiHaler inhalation device. (See **Patient's Instructions for Use**) Spiriva capsules should only be administered via the HandiHaler device and the HandiHaler device should not be used for administering other medications.

Capsules should always be stored in sealed blisters and only removed immediately before use. The blister strip should be carefully opened to expose only one capsule at a time. Open the blister foil as far as the *STOP* line to remove only one capsule at a time. The drug should be used immediately after the packaging over an individual capsule is opened, or else its effectiveness may be reduced. Capsules that are inadvertently exposed to air (i.e., not intended for immediate use) should be discarded.

Eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema may be signs of acute narrow-angle glaucoma. Should any of these signs and symptoms develop, consult a physician immediately. Miotic eye drops alone are not considered to be effective treatment.

Care must be taken not to allow the powder to enter into the eyes as this may cause blurring of vision and pupil dilation.

Spiriva HandiHaler is a once-daily maintenance bronchodilator and should not be used for immediate relief of breathing problems, i.e., as a rescue medication.

Drug Interactions

Spiriva has been used concomitantly with other drugs commonly used in COPD without increases in adverse drug reactions. These include sympathomimetic bronchodilators, methylxanthines, and oral and inhaled steroids. However, the co-administration of Spiriva with other anticholinergic-containing drugs (e.g., ipratropium) has not been studied and is therefore not recommended.

Drug/Laboratory Test Interactions

None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was observed in a 104-week inhalation study in rats at tiotropium doses up to 0.059 mg/kg/day, in an 83-week inhalation study in female mice at doses up to 0.145 mg/kg/day, and in a 101-week inhalation study in male mice at doses up to 0.002 mg/kg/day. These doses correspond to 25, 35, and 0.5 times the Recommended Human Daily Dose (RHDD) on a mg/m^2 basis, respectively. These dose multiples may be overestimated due to difficulties in measuring deposited doses in animal inhalation studies.

Tiotropium bromide demonstrated no evidence of mutagenicity or clastogenicity in the following assays: the bacterial gene mutation assay, the V79 Chinese hamster cell mutagenesis assay, the chromosomal aberration assays in human lymphocytes *in vitro* and mouse micronucleus formation *in vivo,* and the unscheduled DNA synthesis in primary rat hepatocytes *in vitro* assay.

In rats, decreases in the number of corpora lutea and the percentage of implants were noted at inhalation tiotropium doses of 0.078 mg/kg/day or greater (approximately 35 times the RHDD on a mg/m^2 basis). No such effects were observed at 0.009 mg/kg/day (approximately 4 times than the RHDD on a mg/m^2 basis). The fertility index, however, was not affected at inhalation doses up to 1.689 mg/kg/day (approximately 760 times the RHDD on a mg/m^2 basis). These dose multiples may be overestimated due to difficulties in measuring deposited doses in animal inhalation studies.

Pregnancy

Pregnancy Category C

No evidence of structural alterations was observed in rats and rabbits at inhalation tiotropium doses of up to 1.471 and 0.007 mg/kg/day, respectively. These doses correspond to approximately 660 and 6 times the recommended human daily dose (RHDD) on a mg/m^2 basis. However, in rats, fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation were observed at inhalation tiotropium doses of ≥ 0.078 mg/kg (approximately 35 times the RHDD on a mg/m^2 basis). In rabbits, an increase in post-implantation loss was observed at an inhalation dose of 0.4 mg/kg/day (approximately 360 times the RHDD on a mg/m^2 basis). Such effects were not observed at inhalation doses of 0.009 and up to 0.088 mg/kg/day in rats and rabbits, respectively. These doses correspond to approximately 4 and 80 times the RHDD on a mg/m^2 basis, respectively. These dose multiples may be overestimated due to difficulties in measuring deposited doses in animal inhalation studies.

There are no adequate and well-controlled studies in pregnant women. Spiriva should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Labor and Delivery

The safety and effectiveness of Spiriva has not been studied during labor and delivery.

Nursing Mothers

Clinical data from nursing women exposed to tiotropium are not available. Based on lactating rodent studies, tiotropium is excreted into breast milk. It is not known whether tiotropium is excreted in human milk, but because many drugs are excreted in human milk and given these findings in rats, caution should be exercised if Spiriva is administered to a nursing woman.

Pediatric Use

Spiriva HandiHaler is approved for use in the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. This disease does not normally occur in children. The safety and effectiveness of Spiriva in pediatric patients have not been established.

Geriatric Use

Of the total number of patients who received Spiriva in the 1-year clinical trials, 426 were <65 years, 375 were 65-74 years and 105 were ≥75 years of age. Within each age subgroup, there were no differences between the proportion of patients with adverse events in the Spiriva and the comparator groups for most events. Dry mouth increased with age in the Spiriva group (differences from placebo were 9.0%, 17.1%, and 16.2% in the aforementioned age subgroups). A higher frequency of constipation and urinary tract infections with increasing age was observed in the Spiriva group in the placebo-controlled studies. The differences from placebo for constipation were 0%, 1.8%, and 7.8% for each of the age groups. The differences from placebo for urinary tract infections were –0.6%, 4.6% and 4.5%. No overall differences in effectiveness were observed among these groups. Based on available data, no adjustment of Spiriva dosage in geriatric patients is warranted.

ADVERSE REACTIONS

Of the 2,663 patients in the four 1-year and two 6-month controlled clinical trials, 1,308 were treated with Spiriva at the recommended dose of 18 mcg once a day. Patients with narrow angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials.

The most commonly reported adverse drug reaction was dry mouth. Dry mouth was usually mild and often resolved during continued treatment. Other reactions reported in individual patients and consistent with possible anticholinergic effects included constipation, increased heart rate, blurred vision, glaucoma, urinary difficulty, and urinary retention.

Four multicenter, 1-year, controlled studies evaluated Spiriva in patients with COPD. Table 1 shows all adverse events that occurred with a frequency of ≥ 3% in the Spiriva group in the 1-year placebo-controlled trials where the rates in the Spiriva group exceeded placebo by ≥ 1%. The frequency of corresponding events in the ipratropium-controlled trials is included for comparison.

Table 1: Adverse Experience Incidence (% Patients) in One-Year -COPD Clinical Trials

Body System (Event)	Placebo-Controlled Trials		Ipratropium-Controlled Trials	
	SPIRIVA [n=550]	Placebo [n=371]	SPIRIVA [n=356]	Ipratropium [n=179]
Body as a Whole				
Accidents	13	11	5	8
Chest Pain (non-specific)	7	5	5	2
Edema, Dependent	5	4	3	5
Gastrointestinal System Disorders				
Abdominal Pain	5	3	6	6
Constipation	4	2	1	1
Dry Mouth	16	3	12	6
Dyspepsia	6	5	1	1
Vomiting	4	2	1	2
Musculoskeletal System				
Myalgia	4	3	4	3
Resistance Mechanism Disorders				
Infection	4	3	1	3
Moniliasis	4	2	3	2
Respiratory System (upper)				
Epistaxis	4	2	1	1
Pharyngitis	9	7	7	3
Rhinitis	6	5	3	2
Sinusitis	11	9	3	2
Upper Respiratory Tract Infection	41	37	43	35
Skin and Appendage Disorders				
Rash	4	2	2	2
Urinary System				
Urinary Tract Infection	7	5	4	2

Arthritis, coughing, and influenza-like symptoms occurred at a rate of ≥3% in the Spiriva treatment group, but were <1% in excess of the placebo group.

Other events that occurred in the Spiriva group at a frequency of 1-3% in the placebo-controlled trials where the rates exceeded that in the placebo group include: *Body as a Whole:* allergic reaction, leg pain; *Central and Peripheral Nervous System:* dysphonia, paresthesia; *Gastrointestinal System Disorders:* gastrointestinal disorder not otherwise specified (NOS), gastroesophageal reflux, stomatitis (including ulcerative stomatitis); *Metabolic and Nutritional Disorders:* hypercholesterolemia, hyperglycemia; *Musculoskeletal System Disorders:* skeletal pain; *Cardiac Events:* angina pectoris (including aggravated angina pectoris); *Psychiatric Disorder:* depression; *Infections:* herpes zoster; *Respiratory System Disorder (Upper):* laryngitis; *Vision Disorder:* cataract. In addition, among the adverse events observed in the clinical trials with an incidence of <1% were atrial fibrillation, supraventricular tachycardia, angioedema, and urinary retention.

In the 1-year trials, the incidence of dry mouth, constipation, and urinary tract infection increased with age. **(see PRECAUTIONS, Geriatric Use)**

Two multicenter, 6-month, controlled studies evaluated Spiriva in patients with COPD. The adverse events and the incidence rates were similar to those seen in the 1-year controlled trials.

In addition to adverse events identified during clinical trials, the following adverse reactions have been reported in the worldwide post-marketing experience: epistaxis, palpitations, pruritus, and urticaria.

OVERDOSAGE

High doses of tiotropium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 mcg tiotropium in 6 healthy volunteers. In a study of 12 healthy volunteers, bilateral conjunctivitis and dry mouth were seen following repeated once-daily inhalation of 141 mcg of tiotropium.

Acute intoxication by inadvertent oral ingestion of Spiriva capsules is unlikely since it is not well-absorbed systemically.

A case of overdose has been reported from post-marketing experience. A female patient was reported to have inhaled 30 capsules over a 2.5 day period, and developed altered mental status, tremors, abdominal pain, and severe constipation. The patient was hospitalized, Spiriva was discontinued, and the constipation was treated with an enema. The patient recovered and was discharged on the same day.

No mortality was observed at inhalation tiotropium doses up to 32.4 mg/kg in mice, 267.7 mg/kg in rats, and 0.6 mg/kg in dogs. These doses correspond to 7,300, 120,000, and 850 times the recommended human daily dose on a mg/m^2 basis, respectively. These dose multiples may be overestimated due to difficulties in measuring deposited doses in animal inhalation studies..

DOSAGE AND ADMINISTRATION

The recommended dosage of Spiriva HandiHaler is the inhalation of the contents of one Spiriva capsule, once-daily, with the HandiHaler inhalation device. (See **Patient's Instructions for Use**)

No dosage adjustment is required for geriatric, hepatically-impaired, or renally-impaired patients. However, patients with moderate to severe renal impairment given Spiriva should be monitored closely (See **CLINICAL PHARMACOLOGY**, Pharmacokinetics, Special Populations and **PRECAUTIONS**)

Spiriva capsules are for inhalation only and must not be swallowed.

HOW SUPPLIED

Spiriva capsules, containing 18 mcg tiotropium, are light green, with TI 01 printed on one side of the capsule and the Boehringer Ingelheim company logo on the other side.

The HandiHaler inhalation device is gray colored with a green button. It is imprinted with Spiriva HandiHaler (tiotropium bromide inhalation powder), the Boehringer Ingelheim company logo, and the Pfizer company logo. It is also imprinted to indicate that Spiriva capsules should not be stored in the HandiHaler device and that the HandiHaler device is only to be used with Spiriva capsules.

Six Spiriva capsules are packaged in an aluminum / PVC / aluminum blister card. One blister card consists of two blister strips, each containing 3 capsules and joined along a perforated-cut line. After using the first capsule, the 2 remaining capsules should be used over the next 2 consecutive days. Capsules should always be stored in the blister and only removed immediately before use. The foil lidding should only be peeled back as far as the *STOP* line printed on the blister foil to prevent exposure of more than one capsule. The drug should be used immediately after the packaging over an individual capsule is opened.

The following packages are available:

carton containing 6 Spiriva capsules (1 blister card) and 1 HandiHaler inhalation device (NDC 0597-0075-06)
carton containing 30 Spiriva capsules (5 blister cards) and 1 HandiHaler inhalation device (NDC 0597-0075-37)

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

The capsules should not be exposed to extreme temperature or moisture. Do not store capsules in the HandiHaler device.

Rx only

Manufactured by:
Boehringer Ingelheim Pharma GmbH & Co. KG
Ingelheim, Germany

Marketed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA
and
Pfizer Inc.
New York, NY 10017 USA

Address Medical Inquiries to:
www.spiriva.com or (800) 542-6257

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Tiotropium bromide is covered by U.S. Patent No. 5,610,163, with other Patents Pending. The HandiHaler inhalation device is covered by U.S. Design Patent No. 355,029.

Date
Identification Number

EXHIBIT B

US005610163A

United States Patent [19]

Banholzer et al.

[11] **Patent Number: 5,610,163**

[45] **Date of Patent: Mar. 11, 1997**

[54] **ESTERS OF THIENYL CARBOXYLIC ACIDS AND AMINO ALCOHOLS AND THEIR QUATERNIZATION PRODUCTS**

[75] Inventors: **Rolf Banholzer**, Ingelheim am Rheim; **Rudolf Bauer**, Wiesbaden; **Richard Reichl**, Ingelheim am Rheim, all of Germany

[73] Assignee: **Boehringer Ingelheim GmbH**, Ingelheim am Rhein, Germany

[21] Appl. No.: **405,111**

[22] Filed: **Mar. 16, 1995**

Related U.S. Application Data

[63] Continuation of Ser. No. 254,324, Jun. 6, 1994, abandoned, which is a continuation of Ser. No. 100,822, Aug. 2, 1993, abandoned, which is a continuation of Ser. No. 838,724, Mar. 13, 1992, abandoned.

[30] **Foreign Application Priority Data**

Sep. 16, 1989 [DE] Germany 39 31 041.8

[51] **Int. Cl.**[6] **A61K 31/435**; C07D 401/00; C07D 451/12

[52] **U.S. Cl.** **514/291**; 514/304; 546/18; 546/91; 546/125

[58] **Field of Search** 546/91, 125; 514/291, 514/304

[56] **References Cited**

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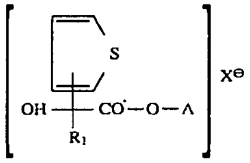
Primary Examiner—Philip I. Datlow
Attorney, Agent, or Firm—Robert P. Raymond; Alan R. Stempel; Mary-Ellen M. Devlin

[57] **ABSTRACT**

Compounds of the formula



of which, in exemplary compounds, the thienyl group is attached via the 2-position and:

(a) A is 3α-(6β, 7β-epoxy)-tropanyl methobromide and R_1 is 2-thienyl;

(b) A is 3α-(6, 7dehydro)-tropanyl methobromide and R_1 is 2-thienyl;

(c) A is 3β-tropanyl methobromide and R_1 is 2-thienyl; and,

(d) A is 3α-(N-isopropyl)-nortropanyl methobromide and R_1 is cyclopentyl.

These are anticholinergics. Administered by inhalation, they are useful for the treatment of chronic obstructive bronchitis or slight to moderately severe asthma. Administered by the intravenous or oral routes, they are useful for the treatment of vagally induced sinus bradycardia.

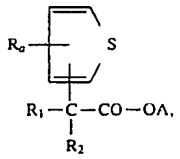
16 Claims, No Drawings

ESTERS OF THIENYL CARBOXYLIC ACIDS AND AMINO ALCOHOLS AND THEIR QUATERNIZATION PRODUCTS

This is a continuation of application Ser. No. 08/254,324, filed on Jun. 6, 1994, now abandoned which is a continuation of application Ser. No. 08/100,822, filed on Aug. 2, 1993, now abandoned, which is a continuation of application Ser. No. 07/838,724, filed on Mar. 13, 1992, now abandoned.

The invention relates to novel thienylcarboxylates of amino alcohols and their quaternary products and to the preparation of the novel compounds and their use as active ingredients in medicaments.

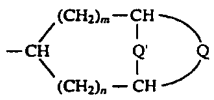
The novel compounds correspond to the formula



(I)

in which

A represents the group



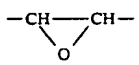
(II)

wherein

m and n independently of one another denote 1 or 2,

Q represents one of the double-bonding groups

$-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH=CH-$,



and

Q' represents the group =NR or the group =NRR', wherein

R denotes H or an optionally halogen-substituted or hydroxy-substituted C_1–C_4-alkyl radical, R' denotes a C_1–C_4-alkyl radical and R and R' together may also form a C_4–C_6-alkylene radical, and wherein, in the case of quaternary compounds, one equivalent of an anion (X^-) opposes the positive charge of the N atom,

R_1 represents a thienyl, phenyl, furyl, cyclopentyl or cyclohexyl radical, wherein these radicals may also be methyl-substituted, thienyl and phenyl may also be fluoro-substituted or chloro-substituted,

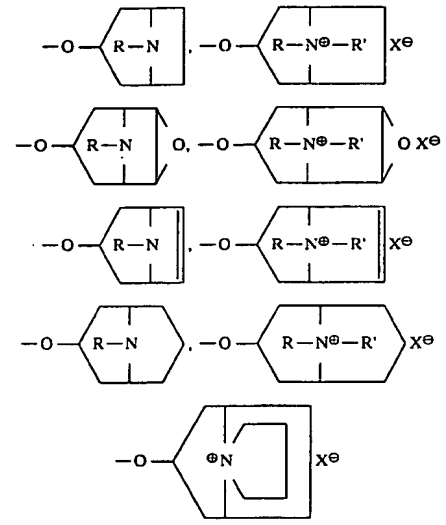
R_2 represents hydrogen, OH, C_1–C_4-alkoxy or C_1–C_4-alkyl,

R_a represents H, F, Cl or CH_3 and, if =NR denotes a secondary or tertiary amino group, also the acid addition salts.

In the compounds of formula I, R_1 preferably represents thienyl, R_2 preferably represents OH. The group —OA preferably has the α-configuration and is derived from, for example scopine, tropine, granatoline or 6,7-dehydrotropine

or the corresponding nor-compounds; however, —OA may also have the β-configuration, as in pseudotropine, pseudoscopine.

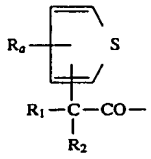
Corresponding radicals are, for example



The substituent R is preferably a lower alkyl radical, such as CH_3, C_2H_5, n-C_3H_7, i-C_3H_7, R' is preferably CH_3. R and R' together are, for example $-(CH_2)_5-$. As halogen substituents for R, F or, as second choice, Cl are suitable.

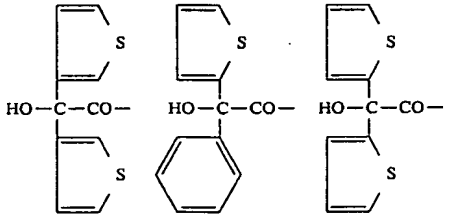
If R denotes a halogen-substituted or hydroxy-substituted alkyl radical, it is preferably $-CH_2-CH_2F$ or $-CH_2-CH_2OH$. Accordingly, the group A represents, for example the radicals of scopine, N-ethylnorscopine, N-isopropylnorscopine, tropine, N-isopropylnortropine, 6,7-dehydrotropine, N-β-fluoroethylnortropine, N-isopropyl-6,7-dehydronortropine, N-methylgranatoline or the corresponding quaternary compounds, wherein the anion is preferably Br^- or $CH_3SO_3^-$.

As the acid radical



(III)

the following are particularly suitable:



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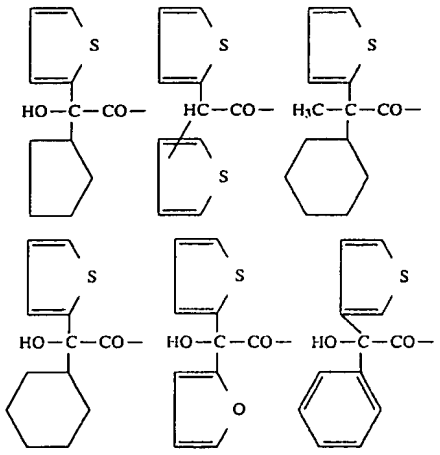


The quaternary compounds are particularly suitable for therapeutic application, whereas the tertiary compounds are important not only as active ingredients but also as intermediate products.

The compounds of the invention are strong anti-cholinergic agents and have prolonged action. Action lasting at least 24 hours is achieved at inhaled dosages in the μg range. In addition, the toxicity is in the same range as the commercial product Ipratropium bromide, while at the same time the therapeutic effect is stronger.

The novel compounds are suitable, in accordance with their anti-cholinergic nature, for example for the treatment of chronic obstructive bronchitis and (slight to moderately severe) asthma, also for the treatment of vagally induced sinus bradycardia.

Whereas application of the novel active ingredients (in particular the quaternary compounds) by inhalation is mainly recommended for respiratory tract diseases, as a result of which side-effects are largely eliminated, the application for sinus bradycardia is preferably carried out intravenously or orally. It has thus proved to be advantageous

that the novel compounds leave the gastro/intestinal motility largely unaffected.

For administration the compounds of the invention are processed using known auxiliaries and/or excipients to give conventional galenic preparations, for example inhalation solutions, suspensions in liquified propellants, preparations containing liposomes or proliposomes, injection solutions, tablets, coated tablets, capsules, inhalation powders for use in conventional inhalation apparatus.

Formulation examples (measures in weight per cent):

1. Controlled dosage aerosol	
Active ingredient according to the invention	0.005
Sorbitan trioleate	0.1
monofluorotrichloromethane and Difluorodichloromethane 2:3	to 100

The suspension is poured into a conventional aerosol container with a dosage valve. 50 μl of suspension are preferably dispensed per actuation. The active ingredient may also be metered in a higher amount if required (for example 0.02 wt. %).

2. Tablets	
Active ingredient according to the invention	0.05
Colloidal silicic acid	0.95
Lactose	65.00
Potato starch	28.00
Polyvinylpyrrolidone	3.00
Na cellulose glycolate	2.00
Magnesium stearate	1.00

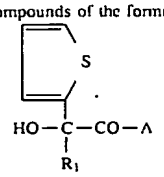
The constituents are processed in conventional manner to give tablets of 200 mg.

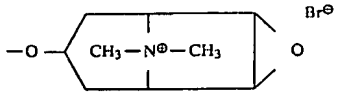
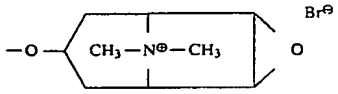
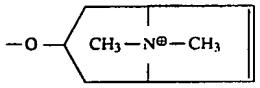
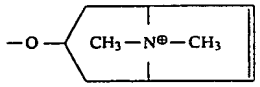
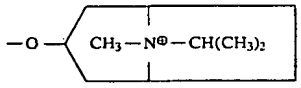
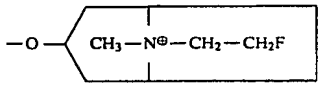
The advantageous properties of the novel compounds are shown, for example, in the inhibition of broncholysis in the rabbit (acetylcholine spasms intravenously). After intravenous administration of the novel active ingredients (dosage 3 μg/kg intravenously), the maximum effect occurred after 10 to 40 minutes. After 5 hours the inhibiting effect had still not been reduced to half, that is to say the half effect time is more, in some cases considerably more, than 5 hours, as made clear by the residual effects after 5 hours listed below:

Compound	Residual effect in %
A	76
B	76
C	81
D	61
E	68
F	73
G	69

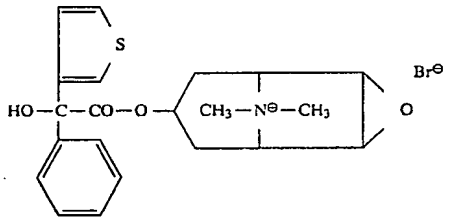
-continued

Compounds of the formula



Compound	A	R_1
A		2-thienyl
B		3-thienyl
D		2-thienyl
E		3-thienyl
F		cyclopentyl
G		cyclopentyl

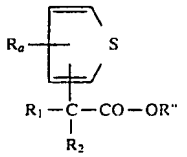
Compound C



Notes:
1. The compounds in which R_1 is not 2-thienyl are racemates.
2. The compounds are 3α-compounds in each case.

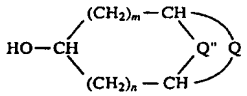
Processes known per se are used to prepare the novel compounds.

An ester of the formula



(IV)

wherein R" represents a C_1–C_4-alkyl radical, preferably a methyl or ethyl radical (R_1, R_2 and R_a have the above meanings), is preferably transesterified using an amino alcohol of the formula



(V)

wherein m, n and Q have the above meanings, Q" represents =NR or =NH and the OH group is in the α- or β-position, in the presence of a conventional transesterification catalyst, and the compound obtained is optionally quaternised

a) if Q" denotes =NR (R≠H) , using a reactive monofunctionalised derivative Z-(C_1–C_4-alkyl) of a corresponding alkane (Z=leaving group)

or is optionally quaternised

b) if Q" denotes =NH, using a terminally disubstituted alkane Z-(C_4–C_6-alkylene)-Z without isolation of intermediates.

The transesterification is carried out with heat in an organic solvent, for example toluene, xylene, heptane, or in a melt, strong bases such as sodium methylate, sodium ethylate, sodium hydride, metallic sodium, being used as catalyst. Reduced pressure is used to remove the released lower alcohol from the equilibrium, the alcohol is optionally distilled off azeotropically. The transesterification takes place at temperatures which in general do not exceed 95° C. Transesterification often proceeds more favourably in a melt. If required, the free bases may be obtained in a manner known per se from acid addition salts of the tertiary amines using suitable basic compounds. Quaternisation is carried out in suitable solvents, for example acetonitrile or acetonitrile/methylene chloride, preferably at room temperature; a corresponding alkyl halide, for example alkyl bromide, is preferably used in the process as quaternising agent. Transesterification products wherein Q' represents NH are used as starting materials for those compounds in which R and R' together represent a C_4–C_6-alkylene group. Conversion into the tertiary and then quaternary compound then takes place with the aid of suitable 1,4-dihaloalkanes, 1,5-dihaloalkanes or 1,6-dihaloalkanes without isolation of intermediates.

The starting materials may be obtained analogously to known compounds—in as much as they have not already been described.

EXAMPLES

methyl di-(2-thienyl)glycolate from dimethyl oxalate and 2-thienyl magnesium bromide;

ethyl di-(2-thienyl)glycolate from (2-thienyl)glyoxylic acid and 2-thienyl lithium;

ethyl hydroxy-phenyl-(2-thienyl)acetate from methyl phenylglyoxylate and 2-thienyl magnesium bromide or from methyl (2-thienyl)glyoxylate and phenyl magnesium bromide.

Methyl 2-thienylglyoxylate and cyclohexyl or cyclopentyl magnesium bromide may be reacted in a similar manner.

Several processes are also available for the preparation of the amino alcohols.

Pseudoscopine may be obtained in accordance with M. Polonovski et al., Bull. soc. chim. 43, 79 (1928). Pseudotropenol may be removed from the mixture (fractional crystallisation or distillation) which is obtained, for example in accordance with V. Hayakawa et al., J. Amer. Chem. Soc. 1978, 100(6), 1786 or R. Noyori et al., J. Amer. Chem. Soc. 1974, 96(10), 3336.

The corresponding methyl esters may be prepared in a conventional manner starting from 2-furylglyoxylnitrile or 3-furylglyoxylnitrile via the 2-furylglyoxylic acid or 3-furylglyoxylic acid which can be obtained therefrom. The corresponding glycolates are obtained from these as described using the organometallic derivatives of 2-bromothiophene or 3-bromothiophene. The organometallic compounds which can be obtained from 2-, 3- or 4-halopyridine can be reacted with methyl 2-thienylglyoxylate or methyl 3-thienylglyoxylate to give the corresponding glycolates.

Thienylglycolates, in which the thiophene ring contains fluorine in the 2- or 3-position, are prepared, for example starting from 2-fluorothiophene or 3-fluorothiophene (bromination to give 2-bromo-3-fluorothiophene or 2-bromo-5-fluorothiophene), and after conversion to the corresponding organometallic compounds, reaction with suitable glyoxylates to give the glycolates.

2-Fluorothiophene and 3-fluorothiophene can be reacted analogously to give the corresponding glyoxylates Unterhalt, Arch. Pharm. 322, 839 (1989) which in turn, as already described, may be reacted with, for example 2-thienyl or 3-thienyl derivatives, to give glycolates. Symmetrically substituted di-thienylglycolates can be prepared analogously by selecting suitable components.

A further route is available via a process analogous to the benzoin condensation and benzilic acid rearrangement.

The following examples illustrate the invention without limiting it.

EXAMPLE 1

EXAMPLE 1

Scopine di-(2-thienyl)glycolate

50.87 g (0.2 mole) of methyl di-(2-thienyl)glycolate and 31.04 g (0.2 mole) of scopine are dissolved in 100 ml of absolute toluene and reacted at a bath temperature of 90° C. with addition of 1.65 g (0.071 gram atom) of sodium in several portions. The resulting methanol is distilled off at a reaction mixture temperature of 78°–90° C. under a pressure of 500 mbar. After a reaction time of about 5 hours, the reaction mixture is stirred into a mixture of ice and hydrochloric acid. The acid phase is separated off, rendered alkaline using sodium carbonate and the free base is extracted using methylene chloride. After drying over sodium sulphate, the methylene chloride is distilled off under reduced pressure and the residue is recrystallised from acetonitrile; beige-coloured crystals (from acetonitrile),

m.p. 149°–50° C.,

Yield: 33.79 g (44.7% of theoretical).

EXAMPLE 2

Scopine di-(2-thienyl)glycolate

12.72 g (0.05 mole) of methyl di-(2-thienyl)glycolate and 7.76 g (0.05 mole) of scopine are melted in a heating bath

at 70° C. under a water jet vacuum. 2.70 g (0.05 mole) of sodium methylate are introduced into this melt and heated for 1 hour in a heating bath at 70° C. under a water jet vacuum and subsequently for a further hour in a heating bath at 90° C. The solidified melt is taken up in a mixture of 100 ml of water and 100 ml of methylene chloride while monitoring the temperature, and the methylene chloride phase is extracted several times using water. The methylene chloride phase is extracted using the corresponding amount of dilute hydrochloric acid. The scopine di-(2-thienyl)glycolate is extracted from the combined aqueous phases using methylene chloride after adding the corresponding amount of sodium carbonate and dried over sodium sulphate. The hydrochloride is prepared from the dried methylene chloride solution in a conventional manner. The crystals are filtered off under suction, washed using acetone and dried under reduced pressure at 35° C. Pale yellow crystals (from methanol), m.p. 238°–41° C. (decomposition);

Yield: 10.99 g (53.1% of theoretical).

The hydrochloride may be converted to the base in a conventional manner.

EXAMPLE 3

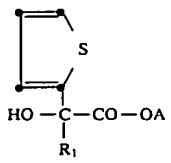
Scopine di-(2-thienyl)glycolate

38.15 g (0.15 mole) of methyl di-(2-thienyl)glycolate and 23.28 g (0.15 mole) of scopine are mixed, 0.34 g (0.015 gram atom) of sodium is added and the mixture is melted in a heating bath at 90° C. under a water jet vacuum. The reaction lasts 2.5 hours. 100 ml of absolute toluene are then added and the mixture is stirred at a heating bath temperature of 90° C. until a solution is produced. The reaction solution is cooled to room temperature and stirred into a mixture of ice and hydrochloric acid cooled using ice. The hydrochloride of the basic ester crystallising out is filtered off under suction and washed using a small amount of water and a large amount of diethyl ether. The filtrate phases are separated off and the aqueous phase is extracted using diethyl ether. The hydrochloride filtered off under suction is suspended in the (acid) aqueous phase and converted to the base while monitoring the temperature and adding the corresponding amount of sodium carbonate; the base is extracted using methylene chloride. The combined methylene chloride phases are dried over sodium sulphate. After distilling off the methylene chloride, crystals remain which are purified over active charcoal and recrystallised from acetonitrile. Pale yellow crystals (from acetonitrile), m.p. 148°–49° C.;

Yield: 39.71 g (70.1% of theoretical).

TABLE I

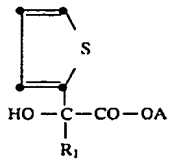
Compounds of the formula



No.	A	R_1	Base	M.p. [°C.] Hydrochloride
1	3α-(6β,7β-epoxy)-tropanyl	2-thienyl	149–50	238–41
2	3α-tropanyl	2-thienyl	167–8	253

TABLE I-continued

Compounds of the formula



No.	A	R_1	Base	M.p. [°C.] Hydrochloride
3	3α-(6,7-dehydro)-tropanyl	2-thienyl	164–5	
4	3α-(N-β-fluoroethyl)-nortropanyl	2-thienyl		236
5	3α-(N-isopropyl)-granatanyl	2-thienyl		232
6	3α-(N-isopropyl)-nortropanyl	2-thienyl		256
7	3α-(6β,7β-epoxy)-N-isopropyl-nortropanyl	2-thienyl		206
8	3α-(6β,7β-epoxy)-N-ethyl-nortropanyl	2-thienyl		212–3
9	3α-(N-ethyl)-nortropanyl	2-thienyl		256–7
10	3α-(N-N-methyl)-granatanyl	2-thienyl		241
11	3α-(6β,7β-epoxy)-N-β-fluoroethylnortropanyl	2-thienyl		188–90
12	3α-(6β,7β-epoxy)-N-n-propylnortropanyl	2-thienyl		104–6
13	3α-(6β,7β-epoxy)-N-n-butylnortropanyl	2-thienyl		225–7
14	3α-(6β,7β-epoxy)-tropanyl	phenyl		246–7
15	3α-tropanyl	phenyl		243–4
16	3α-(N-β-fluoroethyl)-nortropanyl	phenyl		219–20
17	3α-(6,7-dehydro)-tropanyl	phenyl		181–3
18	3α-(N-ethyl)-nortropanyl	phenyl		231–2
19	3α-(N-isopropyl)-nortropanyl	phenyl		246–7
20	3α-tropanyl	cyclohexyl		260
21	3α-(N-β-fluoroethyl)-nortropanyl	cyclohexyl		203–4
22	3α-(6β,7β-epoxy)-tropanyl	cyclopentyl		237
23	3α-tropanyl	cyclopentyl		260
24	3α-(N-β-fluoroethyl)-nortropanyl	cyclopentyl		182–3
25	3α-(N-ethyl)-nortropanyl	cyclopentyl		227–8
26	3α-(N-isopropyl)-nortropanyl	cyclopentyl		174–5
27	3α-(6β,7β-epoxy)-tropanyl	2-thienyl		240–2
28	3β-tropanyl	2-thienyl		217–9
29	3β-(6,7-dehydro)-tropanyl	2-thienyl		233–5
30	3α-(6,7-dehydro)-trapanyl	3-thienyl		247–8
31	3α-(6β,7β-epoxy)-tropanyl	3-thienyl		242–3
32	3α-(6β,7β-epoxy)-tropanyl	2-furyl		
33	3α-(6,7-dehydro)-tropanyl	2-furyl		
34	3α-tropanyl	2-furyl		
35	3α-tropanyl	2-pyridyl		
36	3α-(6β,7β-epoxy)-tropanyl	2-pyridyl		
37	3α-(6,7-dehydro)-tropanyl	2-pyridyl		
38	3α-tropanyl	3-thienyl		
39	3α-(6,7-dehydro)-tropanyl	cyclopentyl		
40	3α-(6β,7β-epoxy)-tropanyl	cyclohexyl		
41	3α-(6,7-dehydro)-tropanyl	cyclohexyl		

Note: All hydrochlorides melt with decomposition.

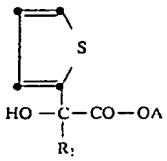
EXAMPLE 4

Scopine di-(2-thienyl)glycolate methobromide

10.0 g (0.0265 mole) of scopine di-(2-thienyl)glycolate are dissolved in a mixture comprising 20 ml of anhydrous methylene chloride and 30 ml of anhydrous acetonitrile and treated with 12.8 g (0.1325 mole) of methyl bromide (as 50% strength solution in anhydrous acetonitrile), and the reaction mixture is allowed to stand for 24 hours at room temperature in a tightly sealed reaction vessel. Crystals are precipitated during this time. They are filtered off under suction, washed using methylene chloride and dried at 35° C. under reduced pressure. White crystals (from methanol/acetone), m.p. 217°–8° C. (decomposition) after drying at 111° C. under reduced pressure.

TABLE II

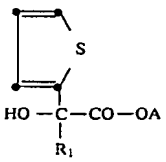
Quaternary compounds of the formula



No.	A	R_1	M.p. [°C.]
1	3α-(6β,7β-epoxy)-tropanyl methobromide	2-thienyl	217–18
2	3α-tropanyl methobromide	2-thienyl	263–64
3	3α-(6,7-dehydro)-tropanyl methobromide	2-thienyl	191–92
4	3α-(N-β-fluoroethyl)-nortropanylmethobromide	2-thienyl	242–43
5	3α-tropanyl-β-fluoroethobromide	2-thienyl	214–15
6	3α-(N-isopropyl)-granatanyl methobromide	2-thienyl	229–30
7	3α-(N-isopropyl)-nortropanylmethobromide	2-thienyl	245–46
8	3α-(6β,7β-epoxy)-N-isopropyl-nortropanyl methobromide	2-thienyl	223–24
9	3α-(6β,7β-epoxy)-N-ethylnortrapanyl methobromide	2-thienyl	215–16
10	3α-(N-ethyl)-nortropanyl methobromide	2-thienyl	260–61
11	3α-(N-methyl)-granatanyl-methobromide	2-thienyl	246–47
12	3α-(6β,7β-epoxy)-N-fluoroethyl-nortropanyl methobromide	2-thienyl	182–83
13	3α-(6β,7β-epoxy)-N-n-propylnortropanyl methobromide	2-thienyl	209–10
14	3α-tropanyl-β-hydroxyethobromide	2-thienyl	231–32
15	3α-(6β,7β-epoxy)-tropanyl ethobromide	phenyl	217–18
16	3α-tropanyl methobromide	phenyl	273–74
17	3α-(N-β-fluoroethyl)-nortrapanylmethobromide	phenyl	
18	3α-(6,7-dehydro)-tropanyl methobromide	phenyl	110–71
19	3α-(N-ethyl)-nortropanyl methobromide	phenyl	249–50
20	3α-(N-isopropyl)-nortropanyl methobromide	phenyl	259–60

TABLE II-continued

Quaternary compounds of the formula



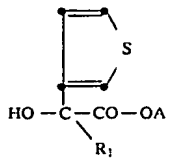
No.	A	R_1	M.p. [°C.]
21	3α-tropanyl ethobromide	phenyl	248–49
22	3α-(N-ethyl)-nortropanyl ethobromide	phenyl	244–45
23	3α-(6β,7β-epoxy)-tropanyl ethobromide	phenyl	226
24	3α-tropanyl-β-fluoroethobromide	phenyl	241
25	3α-tropanyl methobromide	cyclohexyl	278
26	3α-(N-β-fluoroethyl)-nortropanyl methobromide	cyclohexyl	198
27	3α-tropanyl-β-fluoroethobromide	cyclohexyl	233–34
28	3α-tropanyl methobromide	cyclopentyl	260
29	3α-tropanyl ethobromide	cyclopentyl	235–36
30	3α-(N-ethyl)-nortropanyl methobromide	cyclopentyl	251–52
31	3α-(N-isopropyl)-nortropanyl-methobromide	cyclopentyl	244–45
32	3α-tropanyl-β-fluoroethobromide	cyclopentyl	189–90
33	3α-(N-β-fluoroethyl)-nortropanyl-methobromide	cyclopentyl	226–27
34	3α-(6,7-dehydro)-tropanyl metho-methanesulphonate	2-thienyl	225–6
35	3α-(6β,7β-epoxy)-tropanyl methobromide	2-thienyl	218–20
36	3α-tropanyl methobromide	2-thienyl	243–4
37	3α-(6,7-dehydro)-tropanyl methobromide	2-thienyl	211–4
38	3α-(6,7-dehydro)-tropanyl methobromide	3-thienyl	182–3*
39	3α-(6β,7β-epoxy)-tropanyl methobromide	3-thienyl	217–8
40	(+) enantiomer of No. 1	2-furyl	
41	(−) enantiomer of No. 1	2-furyl	
42	3α-(6β,7β-epoxy)-tropanyl methobromide	2-furyl	
43	3α-(6,7-dehydro)-tropanyl methobromide	2-furyl	
44	3α-tropanyl methobromide	2-furyl	
45	3α-(6β,7β-epoxy)-tropanyl methobromide	2-pyridyl	
46	3α-(6,7-dehydro)-tropanyl methobromide	2-pyridyl	
47	3α-tropanyl methobromide	2-pyridyl	
48	3α-tropanyl methobromide	3-thienyl	
49	3α-(6,7-dehydro)-tropanyl methobromide	cyclopentyl	
50	3α-(6β,7β-epoxy)-tropanyl methobromide	cyclohexyl	
51	3α-(6,7-dehydro)-tropanyl methobromide	cyclohexyl	
52	3α-(6β,7β-epoxy)-tropanyl methobromide	cyclopentyl	

*contains crystalline methanol

Note: All compounds in the table melt with decomposition.

TABLE III

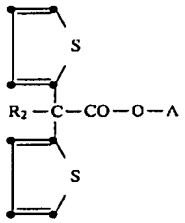
Compounds of the formula



No.	A	R_1	M.p. [°C.] Hydrochloride
1	3α-(6β,7β-epoxy)-tropanyl	phenyl	246–7
2	3α-(6,7-dehydro)-tropanyl	phenyl	261–2
3	3α-(6β,7β-epoxy)-tropanyl	3-thienyl	
4	3α-(6,7-dehydro)-tropanyl	3-thienyl	
5	3α-tropanyl	3-thienyl	
6	3α-(N-methyl)-granatanyl	3-thienyl	

TABLE IV

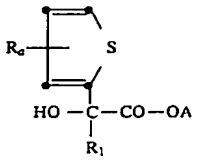
Compounds of the formula



No.	A	R_2	M.p. [°C.] Hydrochloride
1	3α-(6β,7β-epoxy)-tropanyl	H	
2	3α-(6,7-dehydro)-tropanyl	H	
3	3α-(6β,7β-epoxy)-tropanyl	methyl	
4	3α-(6,7-dehydro)-tropanyl	methyl	210–2.5
5	3α-(6β,7β-epoxy)-tropanyl	methoxy	
6	3α-(6,7-dehydro)-tropanyl	methoxy	

TABLE V

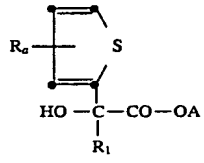
Compounds of the formula



No.	A	R_2	R_a	M.p. [°C.]
1	3α-(6β,7β-epoxy)-tropanyl	2-thienyl	5-methyl	
2	3α-(6,7-dehydro)-tropanyl	2-thienyl	5-methyl	
3	3α-tropanyl	2-thienyl	5-methyl	
4	3α-(6β,7β-epoxy)-tropanyl	2-(5-methyl)-thienyl	5-methyl	
5	3α-(6,7-dehydro)-tropanyl	2-(5-methyl)-thienyl	5-methyl	
6	3α-tropanyl	2-(5-methyl)-thienyl	5-methyl	
7	3α-(6β,7β-epoxy)-tropanyl	2-thienyl	5-fluoro	
8	3α-(6,7-dehydro)-tropanyl	2-thienyl	5-fluoro	
9	3α-tropanyl	2-thienyl	5-fluoro	
10	3α-(6β,7β-epoxy)-tropanyl	2-(5-fluoro)-thienyl	5-fluoro	
11	3α-(6,7-dehydro)-tropanyl	2-(5-fluoro)-thienyl	5-fluoro	
12	3α-tropanyl	2-(5-fluoro)-thienyl	5-fluoro	

TABLE VI

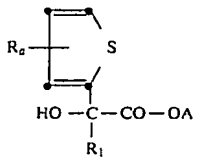
Compounds of the formula



No.	A	R_1	R_a	M.p. [°C.]
1	3α-(6β,7β-epoxy)-tropanyl methobromide	2-thienyl	5-methyl	
2	3α-(6,7-dehydro)-tropanyl methobromide	2-thienyl	5-methyl	
3	3α-tropanyl-methobromide	2-thienyl	5-methyl	
4	3α-(6β,7β-epoxy)-tropanyl methobromide	2-(5-methyl)-thienyl	5-methyl	

TABLE VI-continued

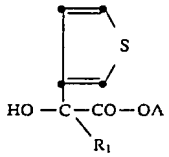
Compounds of the formula



No.	A	R_1	R_a	M.p. [°C.]
5	3α-(6,7-dehydro)-iropanyl methobromide	2-(5-methyl)-thienyl	5-methyl	
6	3α-tropanyl methobromide	2-(5-methyl)-thienyl	5-methyl	
7	3α-(6β,7β-epoxy)-tropanyl methobromide	2-thienyl	5-fluoro	
8	a-(6,7-dehydro)-tropanyl methobromide	2-thienyl	5-fluoro	
9	3α-tropanyl methobromide	2-thienyl	5-fluoro	
10	3α-(6β,7β-epoxy)-tropanyl methobromide	2-(5-fluoro)-thienyl	5-fluoro	
11	3α-(6,7-dehydro)-tropanyl methobromide	2-(5-fluoro)-thienyl	5-fluoro	
12	3α-tropanyl methobromide	2-(5-fluoro)-thienyl	5-fluoro	

TABLE VII

Compounds of the formula

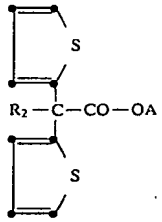


No.	A	R_1	M.p. [°C.]
1	3α-(6β,7β-epoxy)-tropanyl methobromide	phenyl	211–2
2	3α-(6,7-dehydro)-tropanyl methobromide	phenyl	158–60*
3	3α-(6β,7β-epoxy)-tropanyl methobromide	3-thienyl	
4	3α-(6,7-dehydro)-tropanyl methobromide	3-thienyl	
5	3α-tropanyl methobromide	3-thienyl	
6	3α-(N-methyl)-granatanyl methobromide	3-thienyl	

*(with crystalline methanol)

TABLE VIII

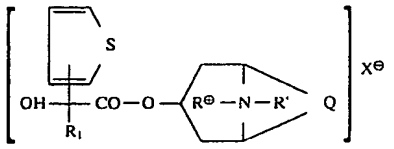
Quaternary compounds of the formula



No.	A	R_2	M.p. [°C.]
1	3α-(6β,7β-epoxy)-tropanyl methobromide	H	
2	3α-(6,7-dehydro)-tropanyl methobromide	H	
3	3α-(6β,7β-epoxy)-tropanyl methobromide	methyl	
4	3α-(6,7-dehydro)-tropanyl methobromide	methyl	206–8
5	3α-tropanyl methobromide	methoxy	
6	3α-(N-methyl)-tropanyl methobromide	methoxy	

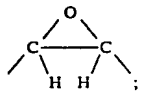
We claim:

1. A compound of the formula



wherein

Q is a group of the formula $-CH_2-CH_2-$, $-CH=CH-$ or

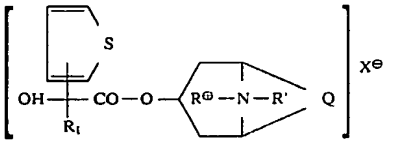


R and R' are each independently C_1–C_4-alkyl;

R_1 is thienyl, phenyl, cyclopentyl or cyclohexyl; and,

X^- is a physiologically acceptable anion.

2. A compound in accordance with claim 1, of the formula



wherein

R is CH_3, C_2H_5, n-C_3H_7, or i-C_3H_7;

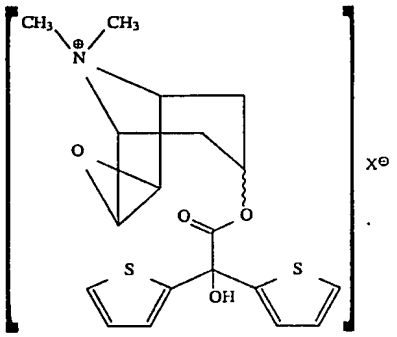
R' is CH_3; and,

R_1, Q and X^- are as defined in claim 1.

3. A compound in accordance with claim 2 wherein R_1 is thienyl.

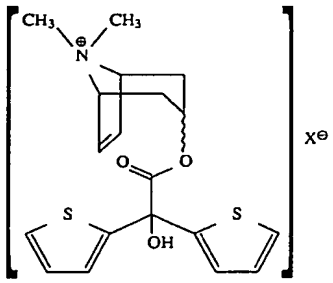
4. A compound in accordance with claim 2 wherein X^- is Br^- or CH_3SO_3.

5. A compound of the formula



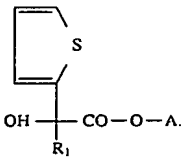
wherein X^- is a physiologically acceptable anion.

6. A compound of the formula

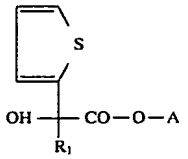


wherein X^- is a physiologically acceptable onion.

7. A compound of the formula

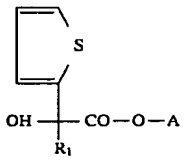


8. A compound of the formula



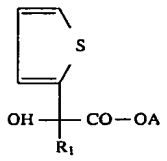
wherein R_1 is 2-thienyl and A is 3α-(6,7-dehydro)-tropanyl methobronide.

9. A compound of the formula



wherein R_1 is 2-thienyl and A is 3β-tropanyl methobromide.

10. A compound of the formula



wherein R_1 is cyclopentyl and A is 3α-(N-isopropyl)-nortropanyl methobromide.

11. A method for treating chronic obstructive bronchitis which comprises administering, by inhalation, to a subject suffering from the same, a therapeutic amount of a compound in accordance with claims 1, 2, 3, 4 6, 7, 8, 9, 10.

12. A method for treating slight to moderately severe asthma which comprises administering, by inhalation, to a subject suffering from the same, a therapeutic amount of a compound in accordance with claims 1, 2, 3, 4, 6, 7, 8, 9, 10.

13. A method for treating vagally induced sinus bradycardia which comprises administering, by the intravenous or oral routes, to a subject suffering from the same, a therapeutic amount of a compound in accordance with claims 1, 2, 3, 4, 6, 7, 8, 9, 10.

14. A pharmaceutical composition, for administration by inhalation, suitable for the treatment of chronic obstructive bronchitis or slight to moderately severe asthma, which comprises a compound in accordance with claims 1, 2, 3, 4, 6, 7, 8, 9, 10.

15. A pharmaceutical composition, for oral administration, suitable for the treatment of vagally induced sinus bradycardia, which comprises a compound in accordance with claims 1, 2, 3, 4, 6, 7, 8, 9, 10.

16. A pharmaceutical composition, for intravenous administration, suitable for the treatment of vagally induced sinus bradycardia, which comprises a compound in accordance with claims 1, 2, 3, 4, 6, 7, 8, 9, 10.

* * * * *

EXHIBIT C

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO : 5,610,163
DATED : March 11, 1997
INVENTOR(S) : Rolf Banholzer, Rudolf Bauer and Richard Reichl

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 18, in the last line of Claim 6, change "onion" to --anion--.

Signed and Sealed this
Fourth Day of July, 2000

Attest:

Attesting Officer

Q. TODD DICKINSON
Director of Patents and Trademarks

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,610,163

DATED : March 11, 1997

INVENTOR(S) : Rolf Banholzer, Rudolf Bauer and Richard Reichl

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the title page item [73], change "Boehringer Ingelheim GmbH" to --Boehringer Ingelheim KG--.

Signed and Sealed this

Thirtieth Day of January, 2001

Attest:

Q. TODD DICKINSON

Attesting Officer

Director of Patents and Trademarks

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,610,163
DATED : March 11, 1997
INVENTOR(S) : Rolf Banholzer, Rudolf Bauer and Richard Reichl

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [73], Assignee, change "**Boehringer Ingelheim GmbH**" to -- **Boehringer Ingelheim KG** --.

Column 18,
Line 25, (immediately following the structural formula and before claim 8), insert -- wherein R_1 is 2-thienyl and A is 3α-(6β, 7β-epoxy)-tropanyl methobromide. --
Line 37, change "methobronide" to -- methobromide --.
Line 63, change "claims 1, 2, 3, 4, 6, 7, 8, 9 10" to -- claims 1, 2, 3, 4, 6, 7, 8, 9 or 10 --.

Column 19,
Line 4, change "claims 1, 2, 3, 4, 6, 7, 8, 9 10" to -- claims 1, 2, 3, 4, 6, 7, 8, 9 or 10 --.
Lines 8 to 9, change "claims 1, 2, 3, 4, 6, 7, 8, 9 10" to -- claims 1, 2, 3, 4, 6, 7, 8, 9 or 10 --.

Column 20,
Lines 1 to 2, change "claims 1, 2, 3, 4, 6, 7, 8, 9 10" to -- claims 1, 2, 3, 4, 6, 7, 8, 9 or 10 --.
Line 6, change "claims 1, 2, 3, 4, 6, 7, 8, 9 10" to -- claims 1, 2, 3, 4, 6, 7, 8, 9 or 10 --.
Line 10, change "claims 1, 2, 3, 4, 6, 7, 8, 9 10" to -- claims 1, 2, 3, 4, 6, 7, 8, 9 or 10 --.

Signed and Sealed this

Third Day of December, 2002

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

EXHIBIT D

United States
Patent and
Trademark Office

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Maintenance Fee Statement

5610163

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,610,163	183	830	0	08/405,111	03/11/97	03/16/95	04	NO	PAID

287

ITEM NBR	ATTY DKT NUMBER
1	1/844-3-C3

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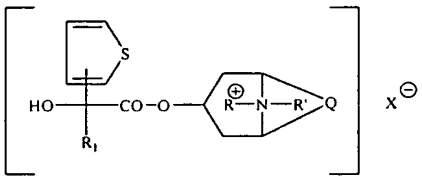
EXHIBIT E

1. A compound of the formula



wherein

Q is a group of the formula $-CH_2-CH_2-$, -CH=CH- or

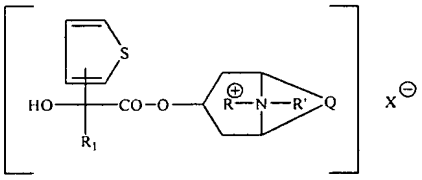
;

R and R' are each independently C_1-C_4-alkyl;

R_1 is thienyl, phenyl, cyclopentyl or cyclohexyl; and,

X^- is a physiologically acceptable anion.

2. A compound in accordance with claim 1, of the formula



wherein

R is CH_3, C_2H_5, n-C_3H_7, or i-C_3H_7;

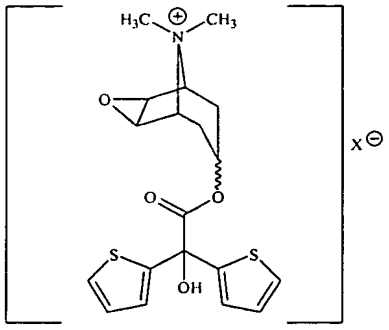
R' is CH_3; and,

R_1, Q and X^- are as defined in claim 1.

3. A compound in accordance with claim 2 wherein R_1 is thienyl.

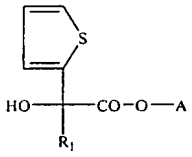
4. A compound in accordance with claim 2 wherein X^- is Br^- or CH_3SO_3.

5. A compound of the formula



wherein X- is a physiologically acceptable anion.

7. A compound of the formula



wherein R_1 is 2-thienyl and A is 3α-(6β, 7β-epoxy)-tropanyl methobromide.

11. A method for treating chronic obstructive bronchitis which comprises administering, by inhalation, to a subject suffering from the same, a therapeutic amount of a compound in accordance with claims 1, 2, 3, 4 6, 7, 8, 9 or 10.

14. A pharmaceutical composition, for administration by inhalation, suitable for the treatment of chronic obstructive bronchitis or slight to moderately severe asthma, which comprises a compound in accordance with claims 1, 2, 3, 4, 6, 7, 8, 9 or 10.

EXHIBIT F

Relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period

(A) The relevant investigational new drug (IND) application, No. 46,687, became effective on 2 February 1995.

(B) The relevant new drug application (NDA), No. NDA 21-395, was initially submitted on 13 December 2001.

(C) The relevant new drug application (NDA), No. NDA 21-395, was approved on 30 January 2004.

EXHIBIT G

SIGNIFICANT ACTIVITIES
UNDERTAKEN BY THE MARKETING APPLICANT
DURING THE
IND PHASE
OF THE REGULATORY REVIEW PERIOD

Date	Submission Type	Abstract
30-Nov-94	ORIGINAL IND SN 000	Quaternary ammonium compound being investigated as long-acting anticholinergic bronchodilator for treatment of patients with reversible airway diseases
08-Dec-94	Agency Contact Report	On 12/8, Dr. Sun of FDA called to get clarification on the recent submission. On 12/9, BIPI confirmed that calculations were present for all inhalation doses and were present in the appendices. Dr. Sun requested table with only the pulmonary doses.
09-Dec-94	Agency Contact Report	FDA called for clinical labels on studies in Germany and Holland.
09-Dec-94	FDA Acknowledgement of Receipt	Submission sent 11/30/94 and received 12/2/94.
12-Dec-94	FAX	Response to call from Dr. Sun of FDA on 12/9/94 regarding clarification of calculations used for determining the theoretical dose to the lung, used for the inhalation studies conducted.
13-Dec-94	Agency Contact Report	Dr. Sun of FDA requested a clarification fo the table faxed to him on 12/12/94.
14-Dec-94	FAX	Regarding 12/13 conversation with FDA, attached updated table containing the theoretical pulmonary doses calculated for the inhalation studies conducted in the rat, dog and mouse.
19-Dec-94	Protocol Amendment: New Investigators SN 001	New Investigators: Prot. # 00921, Drs. Aurerbach, Bode, Campbell, Dunn, Ilowite, Littner, Taskin and
05-Jan-95	Agency Contact Report	FDA sent a fax dated 1/5 to resolve issues on clinical protocol. Outcome of discussions are in BIPI fax to FDA dated 1/6.
05-Jan-95	FAX	From FDA to resolve issues on the clinical protocol.
05-Jan-95	General Correspondence	As requested by FDA enclosed are Fo2 Inhalers #27.1 (RM 1452-2-2), #27.3 (RM 1452-2-3), #27.3 (RM 1452-3-2), 51 capsules.
06-Jan-95	Agency Contact Report	Dr. Sun of FDA called 1/6 and 1/10 to get information on the KCS seen in the dog toxicology
06-Jan-95	FAX	Response to January 5, 1995 Fax from FDA (includes Protocol addendum).
10-Jan-95	FAX	To Drs. Schillings and Bispham of BIGmbH informing them of fax to FDA in which BIPI sent requested labels from the clinical studies conducted in Netherlands (U94-0198) and in Germany (U93-
10-Jan-95	Agency Contact Report	The FDA clinical team met on 1/10 to discuss outcome of their review and they faxed a list of 13 issues. These issues were discussed on 1/11. The outcome of these discussions were faxed to FDA on 1/12. FDA confirmed that this completed all obligations to IND and to allow the initiation of
10-Jan-95	FAX	called Dr. Sun of FDA in response to his calls of 1/6 and 1/10 regarding his request for clarification on the KCS reported in the 5 ug/kg/day dose study #U91-0510 (13-week oral study in dogs), and the absence of KCS in the 4ug/kg/day dose in study #U91-0494 (4-week I.V. study in dogs).
12-Jan-95	FAX	BIPI has provided FDA minutes of telephone conference call to discuss clinical issues presented in facsimile from Drs. Pina and Himmel dated 1/10.

27-Jan-95	Protocol Amendment: New Investigators SN 002	New Investigator, Prot. #00921, Dr. M. Friedman.
02-Feb-95	FAX	FDA has completed review of IND and BIPI may proceed. IND effective February 2, 1995. FDA requests additional information.
06-Feb-95	FDA Request for Information (rec'd by mail; follow-up of February 2, 1995 Fax)	FDA has completed review of the IND and the study may proceed. The enclosed recommendations and requests for additional information is required.
21-Mar-95	Protocol Amendment: New Investigators SN 003	New Investigator,Dr. Joseph Broughton,"Randomized, Multiple-Dose, Double-Blind, Parallel Group Study to Determine the Optimal Dose of Ba679 BR Inhaled as powder in Patients
22-Aug-95 31-Aug-95	Agency Contact Report	Called Dr. Sun of FDA to tell him that the ongoing male mouse carcinogencity study being conducted at BIKG is in week 58 and unexpected mortality is noted at the MId and High dose levels as included in
04-Jan-96	Agency Contact Report	Drug induced mortality on mouse male repeat carcinogenicity study on-going in Germany
11-Jan-96	Agency Contact Report	BA 679 Two Year Mouse Carcinogenicity Study - Dr. Joe DeGeorge of the FDA Supervisory Pharmacologist of Oncology), Chairperson the FDA Cancinogenicity Committee called as a follow-up of my conversation with Dr. Joseph Sun (supervisory Pharmacologist of Pulmonary).
23-Feb-96	Agency Contact Report	Dr. S. Tripati has requested a summary table for PK data for all animals/routes/doses provided in the IND.
19-Mar-96	FAX	PK Table draft outline, and request for a 3/20/96 morning telephone call with Drs. Tripati and Sun. Table contains summary data already in U91-0236, U91-0491. BIPI askes for FDA feedback of table format and content prior to adding data to other PK
02-Apr-96	FAX	PK Table outline data for animal studies.
11-Apr-96	Agency Contact Report	Informed Dr. Tripathi of FDA the route of administration employed in ongoing mouse carcinogenicity study was via inhalation
16-Apr-96	FDA Request for Information	Request for annual report
25-Apr-96	Annual Report SN 004	Reporting period December 13, 1994 - December 31,
16-Sep-96	FDA Request for Information	Attached is BIPI's correspondence with Dr. J. Sun held during the IND review in December 1994 regarding information on deposition factor for pre-clinical inhalation studies conducted, these data were sent to him on 12/12/94
19-Sep-96	General Correspondence SN 005	Response to FDA fax of 9/12/96: information on deposition factor for pre-clinical inhalation studies conducted
26-Sep-96	Information Amendment: Clinical SN 006	Clinical report,U96-3068
16-Oct-96	Request for Meeting SN 007	Initial request for end of phase II meeting, to initiate scheduling of meeting for the end of November 1996
17-Oct-96	FAX	FAX to Cathy Schumaker: initial request of end-of-phase II meeting
24-Oct-96	Request for Meeting SN 008	Request for End-of-Phase II Meeting Package
24-Oct-96	Response to FDA Comments SN 009	BIPI response to items 1 to 13, pertaining to clinical section. (Tiotropium Powder Inhalation System)

29-Oct-96	Agency Contact Report	Cathie Schumaker called and said earliest end of phase 2 meeting could be scheduled is 12/3/96 from 3:00 to 5:00, Peter Fernandes will call back FDA to
30-Oct-96	FAX	Telefax from FDA Confirming meeting December 3,
05-Nov-96	Meeting Package SN 010	Pharmacology and toxicology summary pre-meeting package volume 3, volume 1 & 2 submitted 10/24/96, Ser.# 008
20-Nov-96	FAX	FAX to FDA: overall human-pharmacokinetic summary of 6 clinical studies previously submitted to the IND and an outline of human-pharmacokinetic studies underway or planned
20-Nov-96	Meeting Package SN 011	Pharmacokinetic summary, pre-meeting package, Vol 4. This is an information package for Clinical Section and Drug Product CMC. Three additional pharmacokinetic reports of study 205.104 (U94-0376), Study 205.120 (U95-0066), and U96-2136.
22-Nov-96	Agency Contact Report	Dr. Brian Rogers, CMC reviewer requested clarification on differences between Handihaler used in report U96-2266 and that used in report U96-2295
22-Nov-96	Agency Contact Report	FDA internal meeting outcome of end of phase 2
26-Nov-96	FDA Comments	Comments from FDA reviewers for discussion at 12/3/96 meeting
05-Dec-96	FAX	FAX to FDA, copy of daily patient record sheet to address issue #7 for real-time diary-records to be given to the patient
20-Dec-96	Meeting Minutes	End-of-Phase 2 Meeting, held 12/3/96 with FDA, regarding chemistry, preclinical, biopharm, clinical, statistics.
20-Dec-96	Meeting Minutes; FAX	End of Phase 2 Meeting minutes.
14-Feb-97	Protocol Amendment: New Protocol and New Investigators SN 012	New protocol, Prot.# 205.114/205.117, A multiple dose comparison of 18 mcg of tiotropium inhalation capsules and placebo in a one-year, double-blind, safety and efficacy study in adults with chronic obsructive pulmonary disease (COPD); New Investigators, Drs. Amin Baughman, Blumberg, Briggs, Cary, Casaburi, Craig, DeFraff, Donohue, Friedman, Kane, Hiller, Karpel, Knoper, Levin, Liu, Mahler, Mandel, Miller, Ramsdell, Skatrud, Tiuwit
14-Feb-97 11-Mar-97	FDA Comments	FDA comments on BIPI comments made at End-of-Phase II meeting including endpoint for QOL analysis, addition of symptoms and activities scores of SGRQ, changes in medication, premature discontinuation, PERFs, PK endpoints.
27-Feb-97	Information Amendment: Clinical SN 013	Clinical report, U96-0240
10-Mar-97	Information Amendment	BIPI's proposal to investigate tiotropium bromide's bronchodilative properties in asthmatic patients
10-Mar-97	FDA Comments SN 014	Response to 3/10/97 general investigative plan & initial protocol for an additional indication other than
11-Mar-97	FDA Comments	Response to BIPI's comments from FDA's comments on end-of-phase II meeting and remaining outstanding issues
02-Apr-97	Meeting Minutes SN 015	Final minutes of end-of-phase 2 meeting of 12/3/96
04-Apr-97	Protocol Amendment: New Investigators SN 016	New Investigators, Drs. Anzueto, Auerbach, Goldman, Prot.#205.114/205.117

09-Apr-97	Information Amendment: Pharmtox SN 017	Pharmacology/Toxicology reports, U95-0136, U95-0137, U95-0138, U95-0177, U95-0221, U95-0222, U95-0471, U96-2493, U95-0485, U94-0368, U94-
21-Apr-97	Protocol Amendment: Change in Protocol SN 018	Change in Protocol, Prot.# 205.201, revised inclusion criteria
23-Apr-97	Protocol Amendment: New Investigators SN 019	New Investigator; Dr Knoper, Protocol 205.115/205.128.
09-Jun-97	Information Amendment: CMC and Protocol Amendment: New Investigators SN 020	CMC amendment for formulation changes to 4.5 9, 18 & 36 mcg; New Investigator, Dr. Noveck, Prot.# 205.201
10-Jun-97	Annual Report SN 021	Reporting period December 14, 1995 - December 13,
13-Jun-97	Protocol Amendment: New Investigators SN 022	New Investigators, Drs. Berger, Corren, Gross, Lazarus, Noveck, Pearlman, Segall, Storms, Prot.#
16-Jun-97	Protocol Amendment: Change in protocol SN 023	Change in Protocol, Prot.# 205.201, revised inclusion criteria
10-Jul-97	Protocol Amendment: New Investigators SN 024	New Investigators, Drs. Grossman, Snyder, Taylor, Volz, Prot.# 205.201
15-Jul-97	Protocol Amendment: New Protocol and New Investigators SN 025	New protocol, Prot.# 205.132, Study of handihaler flow rater characteristics in patients with COPD; New Investigator, Dr. Chodosh, Prot.# 205.132
17-Jul-97	Protocol Amendment: New Protocol SN 026	New Protocol, Prot.# 205.202, Study to assess the safety and efficacy of patients with moderate to severe asthma who suffer from nocturnal symptoms; New Investigators, Drs. Beamis, Busse, Grossman, Hudgel, Israel, Lewis, Nathan, San Pedro, Schenkel, Smith, Tashkin, Prot.# 205.202
31-Jul-97	FDA Comments	Comments on protocol 205.202
12-Aug-97	FDA Comments	Response to 4/9/97 submission regarding embryocidal and fetotoxic activity in preclinical data
03-Sep-97	Agency Contact Report	Inquired on division's concerns regarding flow rate study, protocol # 205.132
29-Sep-97	Protocol Amendment SN 027	Information regarding St. Mary's Questionnaire, randomization. Protocol amendment for 205.202, entitled, The effects of tiotropium in patients with nocturnal asthma.
07-Oct-97	Response to FDA Request for Information	Sent statement from BIPI toxicologist regarding comments of FDA fax of August 12, 1997. Changes will be formally submitted to IND, along with additional rat oral range finding Setment I and III
07-Oct-97	Agency Contact Report	Inform FDA on our response to August 12 fax and on the 2 preliminary oral dose range studies to be submitted shortly to the IND.
07-Oct-97	Protocol Amendment: New Investigators SN 028	New Investigators, Drs. Chervinsky, Martin, Taylor Prot.# 205.202
09-Oct-97	Response to FDA Request for Information SN 029	Toxicology statement to answer FDA questions.
10-Oct-97	Information Amendment: Pharmtox SN 030	Pharmacology, Toxicology amendment providing for 2 additional preliminary rat oral range findings (U90-0539 and U90-0540). Route of administration in man is by inhalation.
24-Oct-97	Response to FDA Request for Information	Responses to FDA fax dated August 12, 1997, regarding 2 preliminary oral dose range studies
05-Nov-97	General Correspondence SN 031	Hard copy of fax sent to Ms. Kuzmik on 11/5/97 provided,fax is in response to FDA discussions on 10/7 & 10/24 regarding supporting historical data on survival following fewer implantations in rats

06-Nov-97	Agency Contact Report	Dr. Tripathi's receipt of fax regarding historical data.
23-Dec-97	Protocol Amendment SN 032	New Investigator, Dr. Noveck, Prot.# 205.202
14-Apr-98	Annual Report SN 033	Reporting period December 13, 1996 - December 13,
23-Apr-98	Safety Report SN 034	1998-001058/Initial, haematuria
28-Apr-98	Agency Contact Report	Setting up the pre-NDA meeting.
06-May-98	Safety Report SN 035	1998-001058/Follow-up, worsening hematuria
12-Jun-98	Information Amendment: Clinical SN 036	Clinical trial Protocols, Prot.# 205.133 & 205.134.
12-Oct-98	Response to FDA Request for Information	Response to FDA hold designation of 10/1/98, detention of 002/001, entry #996-0421956-0.
27-Oct-98	Protocol Amendment SN 037	New protocols, Prot.# 205.130 and 205.137, A multiple dose comparison of tiotropium inhalation capsules, salmeterol inhalation aerosol and placebo in a six-month, double-blind, double-dummy, safety and efficacy study in patients with chronic obstructive pulmonary disease (COPD), protocol 205.130 a 12 hour pulmonary function test will be conducted and for protocol 205.137 a 3 hour pulmonary function test
12-Feb-99	Safety Report SN 038	1998-001058/Follow-up, hematuria.
04-Mar-99	Request for Meeting	Request for a Pre-NDA meeting, proposed agenda is attached.
05-Mar-99	Protocol Amendment: New Investigators SN 039	New Investigators, Drs. Donohue, Ilowitz, Lapidus, Taylor Ziment, Prot.#205.130; New Investigators, Drs. Enright, Rodarte, Prot.# 205.137.
05-Mar-99	Request for Meeting SN 040	Request for a Pre-NDA meeting. Proposed agenda and estimated duration for each section is attached.
15-Mar-99	Request for Meeting SN 041	Pre-NDA meeting request and meeting package. BI is targeting an NDA submission for tiotropium powder inhalation system in December, 1999. This meeting package contains summary information and specific questions on the topics listed in the proposed agenda.
26-Apr-99	Safety Report SN 042	Follow-up report: 1998-001058. Study 205.127
28-Apr-99	General Correspondence	Drug product samples for pre-NDA meeting. HandiHaler device (lot# 9602001) Placebo Inhalation Capsules (lot# 9602001). Also provided is the lost for attendees for the CMC meeting on May 10, 1999 and the general meeting of May 12, 1999.
28-Apr-99	FAX	Enclosed is the cover letter to the package being sent via FedEx which contains drug product samples of the HandiHaler and Placebo Capsules. Also enclosed is the list of attendees for the CMC and General Pre-NDA meeting, which will be held in May 10, and 12.
29-Apr-99	Annual Report SN 043	Information amendment clinical - investigator's brochure. Version 6 of the IB dated September 1, 1998 (U92-0551). For the reporting period December 14, 1997 to December 13, 1998.
04-May-99	Information Amendment: Clinical SN 044	13 week portions nof the following two phase III clincal reports: U98-3105 and U98-3142.
05-May-99	General Correspondence SN 045	Enclosed is an addendum to the CMC section of the Pre-NDA meeting package for item 5.0 primary packaging material.
06-May-99	FAX	Attendees and room number for pre-NDA meeting for tiotropium on 5/10/99 and 5/12/99.

20-May-99	Meeting Minutes; General Correspondence SN 046	Tiotropium Br Powder Inhalation System. Copy of BIPIs Pre-NDA Meeting Minutes, CMC & General, held May 10 and May 12, 1999 with FDA. These BI minutes reflect BIs understanding of the agreements and discussions reached during the Pre-NDA
25-May-99	Agency Contact Report	the complete final carcinogencity study reports can be submitted to the IND for the CAC review and the electronic carcinogencity datasets can be submitted with the NDA.
18-Jun-99	Meeting Minutes	CMC pre-NDA minutes for 5/10/99 meeting.
29-Jul-99	Protocol Amendment: New Protocol SN 047	BIPI is amending this IND to provide for a new protocol. Enclosed is protocol 205.1[illegible]1 and
02-Aug-99	Meeting Minutes	Pre-NDA industry meeting minutes of 5/12/99 between the division of Pulmonary drug products and
02-Aug-99	Agency Contact Report	Feedback regarding start of protocol 205.1[illegible]1, notify potential delay to NDA.
09-Aug-99	Protocol Amendment: New Investigator SN 048	Enclosed is investigator documentation for new investigators who are conducting studies for protocol 205.1[illegible]1. This protocol was submitted July 29, 1999, Serial No. 047.
27-Aug-99	Agency Contact Report	Tiotropium: FDA acceptability regarding start of protocol 205.1[illegible]1. FDA agreement to review and comment on dyspnea. New MRO Dr. Eugine
01-Dec-99	Protocol Amendment SN 049	This submission provides for Amendment 2 (9/2[illegible]/99) to Protocol 205.1[illegible]1 to redefine calculation of trapped air volume, to clarify recording of pulmonary function parameters and to adjust time windows as requested by study sites.
17-Dec-99	Protocol Amendment SN 050	New Investigators: enclosed is investigator documentation for Dr. Rodarte who is conducting study 205.1[illegible]1. Also enclosed is investigator documentation for Dr. Zibrack who is conducting
22-Dec-99	Safety Report; FAX	IND Safety report, 1999-00[illegible]185, adverse events: Tachycardia ventricular.
29-Dec-99	Safety Report SN 051	Initial report, 1999-00[illegible]185, adverse events: Tachycardia ventricular.
04-Jan-00	Agency Contact Report	General questions on registration strategy for HandiHaler device and on requirements for PAI for HandiHaler.
05-Jan-00	Safety Report SN 052	1999-00[illegible]185, adverse events: Tachycardia
07-Jan-00	Information Amendment SN 05[illegible]	Pharmacology/Toxicology: BIPI is amending the IND to provide for 16 nonclinical reports. U97-27[illegible]0, U98-2292, U98-2[illegible]86, U98-2850, U98-2851, U98-2879, U99-0166, U99-0167, U99-0205, U99-1[illegible]22, U99-1[illegible]36, U99-1[illegible]47, U99-1[illegible]49, U99-1[illegible]57, U99-1[illegible]58,
10-Jan-00	FAX	Submissions which need Serial No. corrections. Ser.# 049 should be 050 and Ser.# 050 should be 051.
10-Jan-00	Information Amendment SN 054	BIPI is amending the referenced IND to provide for the following clinical reports: U98-[illegible]067 and U99-
10-Jan-00	Information Amendment SN 055	BIPI is amending the referenced IND to provide for an updated Investigators Brochure.
25-Jan-00	7 Day Alert; Safety Report; FAX	1999-002158, adverse events: Sudden death.
26-Jan-00	IND Safety Report SN 056	Initial report: 1999-002158, adverse events: Sudden death.

23-Feb-00	Protocol Amendment SN 057	BIPI is amending this IND to provide for a new protocol. Enclosed is a Phase IIIb protocol (205.218) entitled, "The effect of tiotropium therapy on airway diameter in patients with COPD (A randomized, double-blind, placebo controlled, parallel group
29-Mar-00	Information Amendment SN 058	BIPI is amending the above referenced IND to provide for the following clinical initial 12-week study reports. U98-3142, U98-3105, U99-0060, U99-
02-May-00	Information Amendment SN 059	Clinical: BIPI is amending the IND to provide the full one-year reports (U99-3169, U99-3170, U00-3113 and U00-3114)
19-Jun-00	FAX Request for Meeting	Request for Type B Clinical meeting, attached is the fax copy of the cover letter on BI's request for a Type B Clinical meeting and the pre-meeting information package.
19-Jun-00	Request for Meeting SN 060	Request for a Type B Clinical Meeting, BIPI is requesting a meeting to review the outcome of the Phase III studies, and in particular to agree on the proposed analysis and presentation of these data to allow appropriate label claims for dyspnea and
26-Jun-00	IND Annual Report SN 061	Reporting period of December 14, 1998 to December 13, 1999 also contains the Investigator's Brochure (U92-0551 Version 7).
07-Jul-00	Information Amendment:CMC SN 062	BIPI is amending this IND to provide for information related to the testing of clinical supplies, enclosed are updated testing specifications for the active and placebo capsules.
13-Jul-00	Safety Report SN 063	Follow-up, 1999-003185, adverse events: Tachycardia ventricular.
02-Aug-00	Protocol Amendment: New Investigator	New Investigator Dr Johnson 205.131
14-Aug-00	Fax Meeting with Health Authority Corresp	Telefax of 7-24-00 meeting minutes
22-Aug-00	Fax - IND Prot Amend - Change in Protocol	Fax: Notification of forthcoming submission, draft protocol amendment for 205.130 and 205.137 to secure a second indication for relief of dyspnea
22-Aug-00	Protocol Amendment: Change in Protocol SN 065	Draft Prot amend: Proposed change in Protocol 205.130 and 205.137 second indication for relief of
30-Aug-00	General Correspondence	BI sent a Fax regarding sending of 7 desk copies to attention of David Hilfiker, FDA for submission dated 8/22/00
30-Aug-00	Fax - General Correspondence	Fax to David Hilfiker, FDA
11-Oct-00	Fax - General Correspondence	FDA Fax comments regarding SN 065 concerning protocol amendments 205.130 and 205.137 and
11-Oct-00	General Correspondence - Protocol Amendment: Change in Protocol	letter from FDA with comments regarding SN 065 and the new NDA
12-Oct-00	Protocol Amendment: New Protocol SN 066	Prot Amend: New protocol and investigator 502.223
13-Oct-00	Protocol Amendment: Change in Protocol SN 067	Final Protocol Amendment (205.130 and 205.137)
13-Oct-00	Fax - General Correspondence - Protocol Amendment	Telefax 10/13/2000 re protocol amendment
20-Oct-00	Information Amendment: Clinical SN 069	Clinical updated IB (u92-0551) Version 8
20-Oct-00	Protocol Amendment: Changes in a Protocol,Protocol Amendment: New Protocol SN 068	Change in protocol 205.234 amend #1

15-Nov-00	Protocol Amendment: Change in Protocol and New Investigator SN 070	Change in Protocol 205.223 New Investigator - Dr. Richard Light
30-Nov-00	Protocol Amendment: New Investigator SN 071	Protocol Amendment 205.218 New Investigators
01-Dec-00	Agency Contact Report	Pharm/Tox review not yet initiated and Executive CAC meets weekly as needed
07-Dec-00	Agency Contact Report	Division informed of final carcinogenicity report being submitted with form request for review by
08-Dec-00	Information Amendment: CMC SN 072	Updated Testing Specification 156 0018 998-06 and Testing Specification 156 0018 998-08
15-Dec-00	Information Amendment: Pharmtox SN 073	3 Carcinogenicity reports
05-Jan-01	Safety Report SN 074	Written follow-up no. 3 for safety report 1999-003185 was submitted.
12-Jan-01	Agency Contact Report	Follow-up status of Dec. 15, 2000 submission (SN 073) Exec. CAC meets every week as neeede.
25-Jan-01 07-Feb-01 05-Mar-01	Agency Contact Report	Status of FDA on-going review of Carcinogencity reports; FDA requests electronic data of SAS datassets, BIPI requests for potential FDA consulation on extent of data needed electronically.
23-Feb-01	Protocol Amendment: New Protocol and Change in Protocol SN 075	New protocol 205.230 and Amendment 1 for protocol 205.230 were submitted.
06-Apr-01	Annual Report SN 076	Reporting period 12/14/99 to 12/13/00
09-Apr-01	Protocol Amendment: New Investigator SN 077	New Investigators for 205.218, 205.223, and 205.234
19-Apr-01	Protocol Amendment: Change in Protocol SN 078	Amendment 3 for protocol 205.218 was submitted.
03-May-01	Agency Contact Report	FDA phoned requesting clarification on Amendment 3 to Protocol 205.218 submission 4/19/01 SN 078
09-May-01	Agency Contact Report	FDA phoned requesting clarification on Amendment 3 to Protocol 205.218 submission 4/19/01 SN 078
12-May-01 22-May-01 23-May-01	Agency Contact Report	BIPI phoned eSub Coordinator to obtain feedback on specific strategies for planned NDA.
25-May-01	Protocol Amendment: Change in Protocol and New Investigator SN 079	Amendment 2 for protocol 205.230 was submitted. Additionally New Investigators for 205.230 were submitted.
29-May-01 30-May-01	Agency Contact Report	BIPI phoned eSub Coordinator on FDAs preference eNDA section TOC should be more detailed than folder structure
12-Jun-01	Agency Contact Report	Contacted FDA to obtain User Fee Number (4162) and NDA Number (21-395)
13-Jun-01	FDA General Regulatory Letter	Fax from FDA with NDA number and User Fee
14-Jun-01	Agency Contact Report	BIPI phoned D. Hilfiker with questions regarding Spiriva Training Kit
15-Jun-01	Agency Contact Report	BIPI phoned FDA and confirmed format and content of Safety section of labeling
03-Jul-01	Health Auth Comments Pharmtox SN 080	Response to FDA request for information on carcinogenicity datasets for 3 studies (U98-2726, U98-2727, U99-1464)
03-Jul-01	Protocol Amendment: Change in Protocol SN 081	Protocol Amendment, amendment 1, 2 and 4. Amendment 1 and 2 were inadvertently never submitted and amendment 4 clarifies a question received by the agency about amendment 3.

06-Jul-01	Protocol Amendment - Change in Protocol SN 082	Protocol amendment 2 for protocol 205.22[illegible] was submitted. This amendment changed inclusion criteria age to extend from less than or equal to 70 to be less than or equal to 75.
20-Jul-01	Agency Contact Report	FDA contacted regarding the submission of the Tradename for evaluation. FDA informed of the upcoming protocol amendment submission (Serial No. 08[illegible]) for protocol 205.266 which included a proposal not to collect non-serious adverse events
2[illegible]-Jul-01	Protocol Amendment: New Protocol SN 08[illegible]	Protocol Amendment for new protocol 205_266 Request for FDA confirmation on acceptability of only collecint SAEs (i.e. non-serious adverse events are not collected). This is a Phase IIIb VA study with exacerbation endpoints.
26-Jul-01	Agency Contact Report	FDA feedback on Protocol 205.266 (SN 08[illegible]) provided. Review of the carcinogenicity datasets (SN 080) is ongoing. Format for stability data provided. Update of the electronic submission proposal will be
0[illegible]-Aug-01	Agency Contact Report	FDA contacted regarding IT related issues for the electronic submission. FDA indicated version 8.5 with [illegible]5/70 DLT tape should be used. Files should not be compressed per Randy Levin - FDA.
14-Aug-01	FDA FAX Comments or Request for Information	FDA provided feedback regarding protocol 205.266 (VA study) which included a proposal to not collect non-serious adverse events. The decision to collect or not collect non-serious AE data is BI's. Info for formatting electronic stability datasets provid
14-Aug-01	Protocol Amendment: New Investigator SN 084	New Investigators for 205.1[illegible]0: Irwin, Jimenez, Casaburi, MacIntyre
2[illegible]-Aug-01	General Correspondence SN 085	BI requested FDA for a formal evaluation of the tradename SPIRIVA. No back-up names were submitted. SPIRIVA has been registered in the U.S.
25-Sept-01 26-Sept-01	Agency Contact Report	CDER esub coordinator contacted regarding eNDA 21-[illegible]95. Reports should only be included once in the eNDA. Reports can be listed multiple times in a TOC. Preference that bookmarks in pdf should be
26-Sep-01	Protocol Amendment: New Investigator and New Protocol SN 086	Protocol Amendment No. 1 and New Investigators for 205.266, Drs. Cooper, Farber, Cote, Fulambarker, Gonzalez_Rothi, Habib, Krumpe, Paulson, Piquette, Rice, Sethi, Sharafkhaneh, Young
01-Oct-01	Agency Contact Report	OPDRA indicated they did not have enough information to evaluate our tradename proposal (2[illegible]Aug01; SN 08[illegible]). A draft package insert is minimally needed and ultimately color mockups
05-Oct-01	IND Safety Report SN 087	Safety Update Medwatch form 2001-NB-TIO[illegible]2
08-Oct-01	Information Amendment: Clinical SN 088	(Asthma) Clinical Reports U98-[illegible]174, U98-[illegible]274, U99-1019
08-Oct-01	General Correspondence SN 089	General Correspondence Request for Pediatric Waiver for NDA 21-[illegible]95
11-Oct-01	Agency Contact Report	BIPI phone FDA Document Control Room to obtain a DMF number; however, FDA does not pre-assign numbers
15-Oct-01	Agency Contact Report	It is possible to send a test esub DLT tape to CDER's Electronic Document Room
15-Oct-01	Agency Contact Report	It is possible to send a test esub DLT tape to CDER's Electronic Document Room

17-Oct-01	Protocol Amendment: New Investigator SN 090	Protocol Amendment - New Investigators 205.266 Drs Gross, Shahbaz-Hasan
18-Oct-01	Agency Contact Report	CDER supports arial and times new roman fonts for an electronic submission.
18-Oct-01	IND Safety Report SN 091	IND Safety Report - Follow-up Report 2001-NB-
22-Oct-01	Agency Contact Report	Submission of the DRAFT package insert will allow the assessment of the Tradename to continue
2[illegible]-Oct-01	Agency Contact Report	The (paper) review copy does not need to include clinical study report appendices 16.1.[illegible] to 16.4 as defined in the ICH Clinical Study Report. Review Copy for Statistical Reviewer can be the same as the Review Copy for the Medical Reviewer.
2[illegible]-Oct-01	Health Auth Comments Labeling SN 092	The Draft Package Insert (24Sep01) version was submitted in order that the assessment of the Tradename, SPIRIVA, can continue
25-Oct-01	Agency Contact Report	The test tape will be processed under the same procedures and on the same systems that would be used if it was the official submission. At completion of test, data will be removed from EDR system.
26-Oct-01	General Correspondence	A test esub DLT tape was submitted to CDER's electronic document room (EDR). The tape contained pharmtox, crt and crf data and is to support the upcoming SPIRIVA eNDA.
29-Oct-01	Agency Contact Report	e test esub DLT tape submitted on October 29, 2001 was successfully loaded by FDA's Electronic Document Room.
29-Oct-01	IND Safety Report SN 09[illegible]	IND Safety Report Follow-up #2 2001-NB-TIO[illegible]2
05-Nov-01	Agency Contact Report	The Review Copies for the upcoming eNDA were confirmed. There is no update regarding the FDA's evaluation of the Tradename, SPIRIVA.
12-Nov-01 14-Nov-01	Agency Contact Report	For the upcoming eNDA, Items 19 (Financial Information) and 20 (Other) should be included in one folder called other"."
12-Nov-01 14-Nov-01 15-Nov-01 16-Nov-01	Agency Contact Report	The eSub Coordinator recommended following the current eSub Guidance for the CMC section, but if we want to use the CTD format we should follow the recently published draft ICH/CTD general considerations guidance until the ICH eCTD guidance is completed.
14-Nov-01	Agency Contact Report	The IND submission for the Pediatric Waiver Request should be cited in the NDA cover letter. There is no update on FDA's evaluation of the carcinogenicity studies. The Division wants the non-annotated version of the labeling to be provided as
16-Nov-01	Agency Contact Report	The FDA statistician is still reviewing and analyzing the tumor datasets. The Division's report has not yet been sent to the CAC committee.
19-Nov-01	Protocol Amendment: New Investigator SN 094	New Investigators 205.266 Drs. Friedman, McCormick, Shigeoka, Gottlieb, Kuschner and
19-Nov-01 27-Nov-01 28-Nov-01	Agency Contact Report	ESub Coordinator was contacted. Subfolders should not be created for labeling components. All files should be included directly in the labeling folder. Each labeling component should be a separate pdf file in the labeling folder.
20-Nov-01	Agency Contact Report	Address for the NDA field copy was confirmed.

28-Nov-01	Agency Contact Report	The current Project Manager will be leaving on December 7, 2001. The new Project Manager will be Tony Zecola.
27-Nov-01 28-Nov-01	Agency Contact Report	CDER's eSub Coordinator was contacted to answer a question about the method validation section.
27-Nov-01 28-Nov-01	Agency Contact Report	Esub Coordinator was contacted. A workaround for indexing folders with large amounts of data was obtained. It is acceptable to create 2 crf tocs and associate 1 index file (.pdx) with each or create a third crf toc which points to the second and third
07-Dec-01	General Correspondence SN 095	An updated electronic submission proposal for the SPIRIVA eNDA was submitted.
10-Dec-01	Agency Contact Report	Notify FDA Document Control Room of SPIRIVA electronic submission and 14 review copies
10-Dec-01	General Correspondence	The User Fee of $309,647, along with FDA Form 3397, was submitted to Mellon Bank. The User Fee for SPIRIVA NDA 21-395 is 4162.
14-Dec-01	Information Amendment: Clinical SN 097	The updated investigator's brochure (U92-0551; Version 9, dated) was submitted.
14-Dec-01	Protocol Amendment:New Investigator and Change in Protocol SN 096	Protocol Amendment: New Investigators for 205.223 (Celli), 205.230 (Diamond) and 205.266 (Anzueto) and Change in Protocol 205.230 (Amendment 3)

SIGNIFICANT ACTIVITIES
UNDERTAKEN BY THE MARKETING APPLICANT
DURING THE
NDA PHASE
OF THE REGULATORY REVIEW PERIOD

NDA 21-395 Spiriva HandiHaler
(tiotropium bromide inhalation powder)

Date	Submission Type	Abstract
12-Dec-01	Original Application	Original NDA 21-395 submission for SPIRIVA (tiotropium bromide inhalation powder) on December 12, 2001. This was a complete electronic NDA.
12-Dec-01	General Correspondence	Peggy Hair in the FDA Document Room was notified the SPIRIVA NDA will arrive on December 13th.
12-Dec-01	FAX	A Fax of the NDA 21395 cover letter was sent to the FDA Project Manager, Tony Zecolla to alert him of its arrival. The NDA shipment consists of one DLT tape and 143 volumes for the paper review copy. This is contained in 16 boxes.
12-Dec-01	NDA sent to Field	The NDA field copy cover letter was submitted to Ms. Irma Rivera along with volumes 1 through 12 (paper review copy versions) from NDA 21395
13-Dec-01	General Correspondence	The first page of the NDA cover letter was stamped on 13Dec01 by the FDA document room.
14-Jan-02	Agency Contact Report	An update on the FDA's evaluation of the Tradename (SPIRIVA) was requested.
4-Feb-02	Agency Contact Report	FDA contacted regarding 45 day review use of trade name possible advisory committee meeting
4-Feb-02	Agency Contact Report	The CDER esub coordinator was contacted for guidance on future electronic submissions to the SPIRIVA NDA 21-395. Hyperlinks across submissions are not needed. The folder/file structure for the 4 month safety update is provided in the esub guidance.
11-Feb-02	Agency Contact Report	45 Day review and potential Advisory Committee Meeting
12-Feb-02	Agency Contact Report	Official filing date for the SPIRIVA NDA is 11Feb02. The Project Manager would give no specifics, but indicated we could make assumptions regarding the filing of the NDA since we had not heard anything negative. The 4Feb02 request (NDA Vol1) is cancelled.
21-Feb-02	Agency Contact Report	FDA request for copy of Application Summary and Phase III Pivotal Studies Table listing investigators and site, number of patients enrolled and completed, and number of protocols in Phase III program
22-Feb-02	Response to FDA Comments or Request for Information	Response to FDA Request for Information from H. W. Ju, M.D., FDA , on February 21, 2002 for copy of Application Summary and Phase III Pivotal Study Tables listing investigators and sites and number of protocols in Phase III program
28-Feb-02	Response to FDA Comments or Request for Information	Response to FDA request of February 21, 2002 to E. Lyons request number of patients at each site for primary studies
1-Mar-02	Agency Contact Report	FDA Request for Information to assist in potential clinical site audit
5-Mar-02	Agency Contact Report	DSI can be given access to an eNDA. DSI requests can be submitted electronically if listed in Public Docket 92S-251 or the esub Guidance. For information requested outside of 21CFR314 one needs to decide if paper or electronic is appropriate.
5-Mar-02	Agency Contact Report	FDA Request for follow-up Clinical Site Audit Information
5-Mar-02	Agency Contact Report	FDA discussion regarding PADAC, NDA Letter, Drug Product Samples, Respimat FDA feedback

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7-Mar-02	Agency Contact Report	With an eNDA original submission, subsequent submissions can be paper or electronic format. The top level folder for all electronic submissions is the NDA number. Organization of all esubs should follow 356h/esub guidance.
7-Mar-02	Agency Contact Report	With an eNDA original submission, subsequent submissions can be paper or electronic format. The top level folder for all electronic submissions is the NDA number. Organization of all esubs should follow 356h/esub guidance.
7-Mar-02	FDA Acknowledgment of Receipt	Fax from FDA dated March 7, 2002 Acknowledgment of Receipt for SPIRIVA NDA 21395
7-Mar-02	FDA Comments or Request for Information	FDA Fax requesting information to assist in their review of NDA 21395
7-Mar-02	FDA Acknowledgment of Receipt	FDA acknowledgment of receipt for SPIRIVA dated 01Dec12 received 01Dec13
18-Mar-02	Response to FDA Comments or Request for Information	Response to Dr. Ju's (Scientific Investigations) Request for Information on March 5, 2002. Data for Dr. James Donohue Center 10 Study 105.114/205.117 was provided.
18-Mar-02	Response to FDA Comments or Request for Information	Response to FDA Request for Information from Dr. Ju on March 5, 2002 requesting information from Dr. Lapidus site 36 conducting study 205.130
18-Mar-02	Response to FDA Comments or Request for Information	Response to FDA Request for Information from Dr. Ju on March 5, 2002 requesting information on Dr. Donohue's site 33 for study 205.130
18-Mar-02	Agency Contact Report	ACR regarding e-mail to Dr. Ju at FDA with 3 site cover letters to be included in March 18, 2002 submission
19-Mar-02	Response to FDA Comments or Request for Information	Response to FDA Request of February 4, 2002 Tony Zeccola requested samples of HandiHaler device and blister cards as Reviewer Aids""
25-Mar-02	Response to FDA Comments or Request for Information	Partial Response to FDA Request for Information dated March 7, 2002 from Tony Zeccola Clinical and Statistical Questions 2-4
25-Mar-02	Response to FDA Comments or Request for Information	Fax cover letter of submission Response to FDA Request for Information dated March 25 2002 to Tony Zeccola
25-Mar-02	Agency Contact Report	FDA contacted Peter Fernandes regarding missing pages in original NDA submission
28-Mar-02	Agency Contact Report	FDA indicated the entire 3/25/02 submission should be resubmitted as the majority of the xpt files could not be opened. The FDA wants to receive pdf files rather than word and also pdf files of the cover letter and 356h.
2-Apr-02	Response to FDA Comments or Request for Information	Replacement Submission for Response to FDA Request for Information dated March 25, 2002. A partial response to FDA's March 7, 2002 Request for Information. Questions 2, 3 and 4 submitted. Data sets (xpt) files submitted could not be opened
3-Apr-02	General Correspondence	Fax to Tony Zeccola regarding 02Apr02 CD-Rom Resubmission of 25Mar02 RIR
3-Apr-02	General Correspondence	Fax to Tom Selnekovic at FDA CDER Electronic Document Room regarding CD-Rom for 02Apr02 Resubmission of 25Mar02 RIR
8-Apr-02	Agency Contact Report	FDA indicated that the Dummy" name was fine and the xpt files opened"

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12-Apr-02	Response to FDA Comments or Request for Information	Complete Response to FDA Request for Information 07Mar02 CMC Question 1 and 25Mar02 telephone contact regarding missing page from report U99-3169 clinical study 205.117
12-Apr-02	Agency Contact Report	Dr. Kaplan asked Tony Zeccola for alternate date to September 11 PADAC Meeting. Date not set by FDA yet. When letter comes, we can ask for date change. He also want to know issues to be discussed.
18-Apr-02	Amendment to Unapproved NDA	4 month safety update for SPIRIVA (tiotropium bromide) NDA 21-395
13-May-02	Agency Contact Report	FDA information that hyperlinks wouldn't open on 4th Month Safety Update submission of 4/18/02. Was paper not electronic.
14-May-02	Response to FDA Comments or Request for Information	Response to Dr. Ju's request of April 24, 2002 regarding clarification of PFT data
22-May-02	Agency Contact Report	BIPI request to change PADAC mtg date, face-to-face to decide critical issues for PADAC mtg, possible packaging material changes for commercial launch in US
28-May-02	General Correspondence	FDA sent invoice for adjusted User Fee
14-Jun-02	General Correspondence	BIPI sent payment for Annual Product and Establishment fees for 2002
17-Jun-02	Agency Contact Report	PADAC Meeting Date September 6 and request for pre-PADAC meeting
19-Jun-02	Amendment to Unapproved NDA	Updated Annotated Package Insert and remove reference to secondary outcomies of exacerbations frequency, health related QOL and rescue beta2 agonist use. Requesting formal PADAC preparatory meeting.
19-Jun-02	Response to FDA Comments or Request for Information	FDA Request for Clinical Information
19-Jun-02	Amendment to Unapproved NDA	Amendment to Pending NDA; Meeting Request; Updated Annotated Package Insert
19-Jun-02	Agency Contact Report	Discussion with Topper and Zeccola regarding PADAC date 9/6, labeling amendment, pre-PADAC meeting request
21-Jun-02	General Correspondence	No pre-PADAC meeting per FDA but will address key issues
25-Jun-02	General Correspondence	Fax to Tony Zeccola re tele on 21June2002 re FDA interactions to clarify issues PADAC prep. BI amend NDA to remove ref secondary claims for exacerbation, health-related QOL and rescue beta2 agonist. Study 205.131 include key outcomes support dyspnea
27-Jun-02	General Correspondence	Table on SPIRIVA FDA Tacking List for NDA 21395
1-Jul-02	Agency Contact Report	BI had the opportunity to unofficially ask Dr. Brian Rogers, FDA Review Chemist assigned to SPIRIVA, about his review of the NDA. Two positive comments; well written and hyperlinking is easy to work with.
8-Jul-02	FDA Comments or Request for Information	Fax from FDA Dr. Ju regarding data verification tables Visit 9 for Study 205.130 Dr. Donohue Center 33
8-Jul-02	General Correspondence	Call from Dr. Ju regarding Donohue 483 form and Magnitude of effort and Magnitude of task followed by fax and response by fax and submission #10
9-Jul-02	General Correspondence	Ref to tele call with Mr. Zeccola on 21June2002 reg FDA interactions with clarification of issues on PADAC preparation. Remove secondary claims for exacerbation, health related QOL and rescue beta2 agonist. Study 205.131 key outcomes in support dyspnea

11-Jul-02	Response to FDA Comments or Request for Information	Fax to FDA Dr. Ju re 483 response from Dr. Donohue and entries for Magnitude of Effort and Task data was accurately captured in CFRs; however, error occurred in study report
16-Jul-02	FDA Comments or Request for Information	Response to FDA Fax Tony Zeccola 19June 02 reg studies 205.114/205.117 and 205.115/205.128 patients measure FEV values at hoome; when were the ECGs obtained and no. of patients who reached peak FEV1 at each post-dosing time
16-Jul-02	Response to FDA Comments or Request for Information	Fax to FDA Dr. Ju re 483 response from Dr. Donohue and entries for Magnitude of Effort and Task data was accurately captured in CFRs; however, error occurred in study report
17-Jul-02	FDA Comments or Request for Information	Fax from Mr. Zeccola requesting impurity profile of tiotropium used in noclinical testing.
18-Jul-02	Response to FDA Comments or Request for Information	Fax to Mr. Zeccola regarding telephone converation on July 17, 2002 concerning amendments to 205.131. Also attached FDA Tracking List
19-Jul-02	FDA Comments or Request for Information	Five questions from Dr. Chowdhury regarding Study 205.131. Questions pertaining to exercise parameters; pimary efficacy variable; endurance time at Day 21; differences in treatment effects on test days 42 and 21; list of protocol submissions
22-Jul-02	FDA Comments or Request for Information	Fax from Dr. Chowdhury requesting number of pregnancies that occurred during clinical studies and outcome of pregnancies
22-Jul-02	General Correspondence	Letter from FDA MaryBet Lopez to pre-announce an inspection at Infracor GMBH, Marl, Germany. Scheduled for September 5-6, 2002
24-Jul-02	Response to FDA Comments or Request for Information	BI provided a complete response to FDA's July 19, 2002 request for information regarding pregnancies in clinical trials.
24-Jul-02	Response to FDA Comments or Request for Information	Response to FDA, Kimberly Topper, request for Listing of Investigators submitted in NDA 21395
25-Jul-02	Response to FDA Comments or Request for Information	A complete response to FDA's July 17, 2002 fax was provided. This was a request for the impurity profile of the tiotropium used in nonclinical testing.
25-Jul-02	General Correspondence	FDA pre-announcement of PAI at RPC and DMV
25-Jul-02	Response to FDA Comments or Request for Information	Response to FDA REquest for Information Fax from FDA 2002-07-19 from Dr. B. Chowdhury requesting information on Study 205.131
25-Jul-02	General Correspondence	FDA pre-announcement of PAI at RPC and DMV
26-Jul-02	FDA Comments or Request for Information	This submission provided a response to the FDA Field Investigation's fax of July 22, 2002 regarding an FDA inspetion at Infracor. This submission included a signed confirmation from Infracor for the proposed inspection date and hotel information.
26-Jul-02	Fax	Fax from FDA asking for combined data discussing heart rate changes
26-Jul-02	General Correspondence	FAX 7-26-02 to FDA regarding site inspection of GMBH scheduled for 9/5-6, 2002
26-Jul-02	Fax	Fax to FDA 7-26-02 regarding 7/24 and 7/25/02 Submissions sent covering pregnancy, 205.131, impurity profile question, and investigators list
30-Jul-02	General Correspondence	Confirmation from Ingelheim and Biberach that proposed dates for respective PAI is acceptable. Hotel confirmation included.

31-Jul-02	Response to FDA Comments or Request for Information	Response to FDA Request for Information Fax dated 26July2002 requesting shift tables indicating number and percent of patients exhibiting specific increase in heart rate at each test day. Provide increases of 5, 10, 15 and 20 beats per minute
31-Jul-02	Fax	Fax to FDA regarding 8/2/02 Telecon to discuss 205.131
2-Aug-02	Response to FDA Comments or Request for Information	This submission responded to FDA Field Investigation's fax of 25Jul02 which pre-announced inspection at RPC Formatec in Mellrichstadt, Germany. A signed letter of confirmation from RPC regarding the proposed inspection dates of 23-27Sep02 was included.
2-Aug-02	Agency Contact Report	Clarification on several issues related to the Pre-approval Inspections at RPC (manufacturer of the HandiHaler device) and DMV International (lactose manufacturer) was requested from the Division of Field Investigations.
2-Aug-02	Agency Contact Report	Telecon with FDA 8-2-02 regarding 205.131
5-Aug-02	Fax	Fax to FDA listing 8-2-02 Telecon participants
6-Aug-02	General Correspondence	Pulmonary-Allergy Drugs Advisory Committee Meeting Briefing Package for September 6, 2002
6-Aug-02	General Correspondence	A copy of the August 6, 2002 cmc amendment (submission #16) was submitted to the FDA field office.
6-Aug-02	Response to FDA Comments or Request for Information	CMC Amendment for the 24-month Stability Report as requested by FDA on June 28, 2002. Includes stability dataset
9-Aug-02	Response to FDA Comments or Request for Information	This submission responded to the FDA Field Office fax of July 25, 2002 which announced a pre-inspection at DMV International in Veghal, The Netherlands on October 16-22, 2002. Hotel information and contact information was provided as requested.
12-Aug-02	Response to FDA Comments or Request for Information Field Copy	This submission responded to the information request of August 02, 2002 from Ms. Rivera in which she requested BI to submit another complete copy of the original NDA field copy.
14-Aug-02	Fax	Fax to Zeccola siting e-mail pdf versions of two references
14-Aug-02	FDA General Regulatory Letter	The FDA Int'l Operations Group has cancelled the inspection at RPC Formatec. A replacement pre-approval inspection is schedule for Institut Fresenius for September 23-24, 2002.
15-Aug-02	Agency Contact Report	Feedback from irma Rivera regarding the inspectors and inspections at RPC and DMV. Inspection at RPC cancelled, replaced with inspection at Institute Fresenius
16-Aug-02	Meeting with Health Authority Corresp	FDA provided, via email, their briefing document for the 06Sep02 Pulmonary & Allergy Drugs Advisory Commitee which will discuss NDA 21395 (SPIRIVA) for the treatment of bronchospasm and dyspnea associated with COPD.
20-Aug-02	Agency Contact Report	Feedback from Lourdes Valentin regarding dates for PAI at Institute Fresenius
22-Aug-02	Response to FDA Comments or Request for Information	BI replied to the August 22, 2002 fax from the FDA Field Investigation Office. A signed letter from Institut Fresenius agreeing to the inspection dates of October 21-22, 2002 was included.
22-Aug-02	FDA General Regulatory Letter	FAX rec'd from FDA confirming inspection of Institut Fresenius, Taunusstein, Germany. Inspection will determine testing of finished dosage following FDA GMP. Proposed date of inspection Oct 21-22, 2002.
25-Aug-02	Agency Contact Report	Feedback from lourdes Valentin re Inspector Kovacs travel.

27-Aug-02	General Correspondence	Mr. John White, FDA Field Investigator called for Eileen Wyka regarding upcoming inspection to BI Ingelheim and Biberach the week of September 9th. Mr. White will bring a chemist along. Mr. White requested two translators available.
27-Aug-02	Agency Contact Report	Feedback from Inspector John White re PAI at Ingelheim and Biberach
3-Sep-02	Agency Contact Report	Cancellation of PAI at Infracor
6-Sep-02	Meeting with Health Authority Corresp	FDA's overheads and other meeting information from The Pulmonary and Allergy Drugs Advisory Committee. The PADAC was held on September 6, 2002 for the SPIRVA NDA 21395.
6-Sep-02	Meeting with Health Authority Corresp	BI's primary presentation to the September 06, 2002 Pulmonary and Allergy Drugs Advisory Committee Meeting.
6-Sep-02	Agency Contact Report	FDA questioned PADAC on safety issues, FDA commented on bronchodilator effect and benefit of dyspnea relief
13-Sep-02	Agency Contact Report	Information regarding rescheduling of PAI at Infracor
17-Sep-02	Agency Contact Report	The esub coordinator was contacted regarding advice on preparing an electronic submission for labeling.
18-Sep-02	FDA Comments or Request for Information	This submission provided a complete response to FDA's request for the June 19, 2002 labeling in an electronic format. This was a complete electronic submission with review aids in the review copy.
18-Sep-02	FDA General Regulatory Letter	FAX from FDA Irma Rivera, Program Specialist, pre-announce an inspection of Infracor GmbH in Marl, Germany on October 11, 2002. Requesting BI assistance in obtaining hotel arrangements. FDA is responsible for paying all lodging and incidental expenses.
24-Sep-02	Response to FDA Comments or Request for Information	Response to FDA Request for Information related to the number of subjects exposed to study drug while enrolled in clinical trials
24-Sep-02	Response to FDA Comments or Request for Information - Fax	Fax to Zeccola that submission RIR clinical trials being sent
25-Sep-02	Response to FDA Comments or Request for Information	Response to FDA Request for Information - remove statement to the best knowledge and belieg of the undersigned" to Item 16 Debarred Persons"
25-Sep-02	Response to FDA Comments or Request for Information	Asking verification of wording and then submission would be sent - debarement statement
25-Sep-02	Agency Contact Report	Feedback re PAI at DMV International
25-Sep-02	Agency Contact Report	Request for FDA comments on labeling and potential Phase IV commitments as recommended at PADAC on 9-6-02
2-Oct-02	Labeling	This submission provided a labeling amendment in response to the BI/FDA tcon held on 25Sep02. The 02Oct02 version of the package insert was included. This was a complete electronic submission.
2-Oct-02	Agency Contact Report	Labeling Amendment containing cover letter as pdf and history and proposed labeling as word files were sent to Mr. Zeccola by secured e-mail
10-Oct-02	Labeling	FDA proposed labeling of October 10, 2002. Response to the BI submission of October 2, 2002.

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11-Oct-02	Agency Contact Report	Telecon with FDA regarding delay in action letter scheduled to be sent 10-11-02 to allow for more review and additional foreign site inspections
17-Oct-02	Fax	Fax to Zeccola with copy of fax to Meyer on Labeling inclusion request for salmeterol data
17-Oct-02	Fax	Request from Marty Kaplan to Bob Meyer to include salmeterol data in labeling
18-Oct-02	Agency Contact Report	e-mails to agency for labeling discussion and telecon set-up
21-Oct-02	Agency Contact Report	FDA feedback on preclinical toxicology labeling and calculation issues
25-Oct-02	Fax	Fax from FDA regarding pharmacology/toxicology issues
29-Oct-02	Agency Contact Report	CDER's esub coordinator was contacted regarding the approach for responding to an action letter with a complete electronic submission.
31-Oct-02	Health Auth Comments CMC	FDA questions to RPC DMF for the HandiHAler
31-Oct-02	Health Auth Comments CMC	FDA comments to RPC Type III DMF 15696 for the HandiHaler device.
19-Nov-02	Labeling	This submission responded to FDA's October 10, 2002 correspondence by providing the 19Nov02 version of the proposed package insert and patient instructions for use. This submission is a complete electronic submission.
19-Nov-02	Fax	Fax to Zeccola regarding 4-week inhalation study for primary degradation products with substantiating documentation from 1999 FDA's Kearny Dunn
27-Nov-02	Response to FDA Comments or Request for Information	SPIRIVA Toxicology qualification degradants/impurities
3-Dec-02	Agency Contact Report	FDA action letter - CMC review completed, site inspection okay, will hold up on labeling as review not completed by agency, 13-week tox exemption under discussion at agency - letter should come 12/13
13-Dec-02	Fax	Fax with Telecon information for 12/16/02 TC between Tony Zeccola and Peter Fernandes regarding status of action letter for SPIRIVA
13-Dec-02	Agency Contact Report	Status of FDA action letter - late due to tight schedule and weather. TC set up for 12/16/02 at 12:30 PM.
13-Dec-02	Agency Contact Report	Status of Action Letter and teleconference set-up with Agency e-mails
16-Dec-02	Fax	Fax to FDA regarding TC for 12/18/02 to discuss status of action letter for SPIRIVA
16-Dec-02	Agency Contact Report	FDA indicated letter being circulated among disciplines. Labeling issues being addressed at Chowdhury's request. Telecon set for Wed., December 18 at 11:30 AM to FDA to update status.
16-Dec-02	Agency Contact Report	e-mails to Agency referencing toxicology issues in an overview by Neil Johnson and a discussion of the values included in the summary version" of Nov. 19 submission"
18-Dec-02	Agency Contact Report	FDA teleconference discussing that the action letter is now with Dr. Meyer for review. No date for sending. Dr. Blank wants to talk to Dr. Meyer if expected to be after Christmas. BIPI upset by lateness.
19-Dec-02	Agency Contact Report	FDA Zeccola said action letter to come before Christmas 2002. Either on 12/23 evening or 12/24 morning e-mailed to Peter by PDF and faxed to BIPI. Peter will distribute.
20-Dec-02	FDA General Regulatory Letter	FDA approvable letter 12-20-02 for SPIRIVA

23-Dec-02	General Correspondence	Response to FDA Approvable Letter: Letter of Intent to File an amendment
14-Jan-03	Agency Contact Report	e-mail to Agency requesting informal meeting to discuss items in Action letter and what is needed for approval of application
17-Jan-03	Amendment to Unapproved NDA,Meeting with Health Authority Corresp - Fax	FAX - BIPI requesting a meeting regarding clarification on CMC comments contained in Approval Letter dated December 20, 2002
17-Jan-03	Amendment to Unapproved NDA,Meeting with Health Authority Corresp	BIPI requesting a meeting regarding clarification on CMC comments contained in the Approval Letter of December 20, 2002
27-Jan-03	General Correspondence	Meeting Pariticipants and Clarification Point Correction contained in Point 9. CMC Meeting set for January 31, 2003
27-Jan-03	Fax	Fax sent to FDA providing BI's participants for CMC Meeting January 31, 2003. Clarification re Point 9 of CMC Discussion Points for Clarification
4-Feb-03	Agency Contact Report	E-mail to FDA Zeccola regarding clarification on promotional material, safety update, and toxicology clarification for labeling.
25-Feb-03	General Correspondence,Response to FDA Comments or Request for Information,Meeting with Health Authority Corresp	CMC Clarification Meeting Minutes - RIR - meeting on January 31, 2003
25-Feb-03	Response to FDA Comments or Request for Information	Meeting minutes; response to FDA request for information - reference to CMC meeting of January 31, 2003
25-Feb-03	Agency Contact Report	e-mails to FDA regarding feedback to Action Letter issues: labeling, toxicology, dose calculations, safety update
27-Feb-03	Agency Contact Report	e-mails regarding SPIRIVA pending FDA issues i.e. promotional material, safety update, toxicology
14-Mar-03	Agency Contact Report	FDA telecon on 3-28-03 to discuss pre-clinical toxicology issues
14-Mar-03	Meeting with Health Authority Corresp	Confirm telephone Conference call between FDA and BI to review specific NDA issues related to pre-clinical toxicology
20-Mar-03	Agency Contact Report	ACR FDA agrees to approve 1-3-5 packaging and wants BI to develop improved packaging for later use
24-Mar-03	Agency Contact Report	In use study with 1-3-5 not required. 3 mth stability for 1-3-5 to be filed 1 mth after BI completes response to approvable letter. 6 mth report due 3 mths later. In 2-3 mths FDA requests update of optimized packaging and overall timeline.
25-Mar-03	Meeting with Health Authority Corresp	FDA telecon mtg minutes with BIPI on March 20th to discuss BI's Feb 25th submission of configuration of internal packaging of Tio capsules. FDA stating that 3 capsules per blister card is not optimal. FDA proposed BI to conduct an in-use stability study
31-Mar-03	Agency Contact Report	e-mail regarding rescheduling of telecon with FDA from March 28 to April 1 at 9:00 AM to discuss toxicology issues.
1-Apr-03	Agency Contact Report	April 1, 2003 teleconference with FDA to discuss toxicology, promotional material and safety update issues and decisions made.
7-Apr-03	General Correspondence	FDA fax with minutes of March 24, 2003 TC discussing 1-3-5 blister pack and stability data to support it.

7-Apr-03	Fax	Fax from FDA with minutes regarding April 1, 2003 TC discussing dose ratios of tio between animals and humans and degradation products in the drug substance and drug product.
23-Apr-03	Agency Contact Report	Discussion with FDA for combining AE reports and asking for feedback on Holter Study with additional e-mails attached.
17-Jun-03	Agency Contact Report	DDMAC information on pre-clearnace promotional material prior to NDA approval relating to SPIRIVA and other drugs
28-Jul-03	Agency Contact Report	E-mail to FDA of cover letter from Response Package being submitted on 7-31-03. Response to December 20, 2002 Action Letter.
31-Jul-03	Response to FDA Comments or Request for Information,Health Auth Comments CMC,Health Auth Comments Labeling,Health Auth Comments Pharm Tox	COMPLETE Response to FDA Action Letter dated December 20, 2002
31-Jul-03	Health Auth Comments CMC,Response to FDA Comments or Request for Information Field Copy	Field Copy of BIPI CMC Response to Approvable Letter of December 20, 2002 (volumes 2 - 4)
31-Jul-03	Response to FDA Comments or Request for Information,Health Auth Comments CMC,Health Auth Comments Labeling,Health Auth Comments Pharm Tox	COMPLETE Response to FDA Action Letter dated December 20, 2002
8-Aug-03	Amendment to Unapproved NDA	REPLACEMENT of Cover Letter to Complete Response to FDA Action Letter of December 20, 2002
11-Aug-03	Agency Contact Report	ACR with e-mail sent to BI and BIPI individuals regarding complete response package submission and cover letter. A formal meeting request is made for October. Discussions to be held 3rd and 4th week in August.
22-Aug-03	Amendment to Unapproved NDA,Health Auth Comments CMC Field Copy	Stability Report
22-Aug-03	Health Auth Comments CMC	This amendment provides for updated stability data (3 months in the Wannenblister 3 count configuration). Reports H008223 and H008221 were submitted. This was a complete electronic submission.
25-Aug-03	Agency Contact Report	Discussion with FDA regarding 3-month stability submission on August 22 and the need for a letter acknowledging the complete response package submission sent on July 31st that should have been sent on August 15th
26-Aug-03	FDA Acknowledgment of Receipt	FDA letter acknowledging receipt on 8/1/03 or 7/31/03 resubmission to NDA. Complete Class 2 Response to 12/12/02 Action letter. User fee goal is 2/1/04.
26-Aug-03	FDA Acknowledgment of Receipt - Fax	Fax from FDA acknowledging receipt of complete response package sent on July 31, 2003
26-Aug-03	Agency Contact Report	Complete response submission letter signed and to be sent today or tomorrow. FDA to work with BI as requested
12-Sep-03	Agency Contact Report	discussion with FDA on status of complete response review and schedule for feedback on labeling

24-Oct-03	Response to FDA Comments or Request for Information,Health Auth Comments Labeling	Actual 1:1 scale 1-3-5 blister label drawings for SPIRIVA capsules to be used for the market. Box of six placebo 1-3-5 blister cards without current proposed labeling.
27-Oct-03	Agency Contact Report	Discussion with Dr. Chowdhury regarding NDA review and labeling decisions. Agreed to teleconference with BIPI Management.
28-Oct-03	Agency Contact Report	Discussion between BIPI and Dr. Chowdhury regarding status of NDA review, CMC review, and possibility of two cycle approval
5-Nov-03	Amendment to Unapproved NDA,Health Auth Comments CMC	Updated CMC Stability Report
5-Nov-03	Amendment to Unapproved NDA,Health Auth Comments CMC Field Copy	CMC Amendment / Updated Stability Report H008330 and H008331
7-Nov-03	Health Auth Comments CMC	FDA CMC IR Letter with 26 questions
7-Nov-03	Health Auth Comments CMC,Health Auth Comments Labeling	FDA IR Letter regarding CMC and Labeling
12-Nov-03	Agency Contact Report	ACR with e-mail from Tony Zeccola indicating that a discussion may be held with Dr. Schroeder once BIPI has indicated a timeframe and a copy of the CMC IR Letter received on November 7, 2003
13-Nov-03	General Correspondence,Health Auth Comments CMC	BIPI requesting a telephone conference with CMC Reviewer to discuss several comments where clarification is required. Reference is made ot Information Request Letter dated November 7, 2003
13-Nov-03	General Correspondence,Health Auth Comments CMC - Fax	FAX - BIPI request for telephone conference for clarification to Information Request dated November 7, 2003
18-Nov-03	Health Auth Comments CMC	FDA fax requesting additional CMC information for the November 20, 2003 face-to-face meeting
20-Nov-03	Agency Contact Report	ACR regarding meeting between FDA chemists and BI tech and regulatory team regarding clarification in the IR letter of November 7, 2003 to discuss CMC and labeling issues.
30-Nov-03	Health Auth Comments CMC - Fax	FDA Fax regarding C of A for foil and question for study 205.131
4-Dec-03	Response to FDA Comments or Request for Information,Health Auth Comments CMC	Response to FDA Request for Information dated November 7, 2003 and November 18, 2003 Fax
5-Dec-03	Health Auth Comments CMC,Response to FDA Comments or Request for Information Field Copy	FIELD COPY of BIPI's Response to FDA Request for Information November 6th Letter and November 18th Fax
10-Dec-03	Health Auth Comments CMC	FDA e-mail letter with 6 CMC questions and 26 Labeling CMC questions
10-Dec-03	Health Auth Comments CMC,Health Auth Comments Labeling	FDA official letter with 6 CMC questions and 20 Labeling questions.
11-Dec-03	Response to FDA Comments or Request for Information,Health Auth Comments Clin PK	Response to FDA Request for Information of November 28, 2003
13-Dec-03	Fax	FDA Fax regarding new container closure system

NDA 21-395 Spiriva HandiHaler
(tiotropium bromide inhalation powder)

16-Dec-03	Labeling	Revised Labeling submitted in response to FDA's November 07, 2003 CMC Information Request Letter. Other outstanding modifications also incorporated into labeling.
16-Dec-03	Response to FDA Comments or Request for Information,Health Auth Comments CMC Field Copy	Field Copy of Submission #29 BIPI Response to FDA Information Request Letter of December 10, 2003
16-Dec-03	Health Auth Comments Labeling,Health Auth Comments CMC	BIPI's complete response to FDA Information Request Letter of December 10, 2003. Labeling amendment to respond to FDA's Information Request Letters of November 07, 2003 (comments 12, 20, 21, 22 and 25) and December 10, 2003.
18-Dec-03	Response to FDA Comments or Request for Information	BI's response to FDA's 15Dec03 telephone information request for labeling was provided. The value of 32.357 mg/kg in mice is correct.
19-Dec-03	Health Auth Comments CMC	FDA CMC questions and comments based on the November 7 and December 4 submissions
23-Dec-03	Health Auth Comments Labeling	Preliminary questions on labeling (Clinical and CMC) - 19 questions
23-Dec-03	Health Auth Comments Clin PK Fax	FDA Fax requesting clinical data
30-Dec-03	Response to FDA Comments or Request for Information,Labeling	Response to FDA Labeling Comments and Information Requests of December 23, 2003
30-Dec-03	Agency Contact Report	E-mail to Tony Zeccola of submission being sent out on 12-30 03 with attachments containing items being submitted to FDA of cover letter, response to labeling and clinical IR along with annotated and clean draft of labeling
5-Jan-04	Response to FDA Comments or Request for Information,Health Auth Comments CMC Field Copy	FIELD COPY - COMPLETE Response to FDA Information Requests of December 19, 2003 and December 23, 2003
5-Jan-04	Health Auth Comments CMC,Response to FDA Comments or Request for Information	COMPLETE Response to FDA CMC Information Request of December 19, 2003 and December 23, 2003
8-Jan-04	General Correspondence	An email was sent to the FDA Project Manager, Tony Zeccola, to inform him of the January 8th labeling submission. The signed cover letter for the January 8th submission was included as an attachment.
8-Jan-04	General Correspondence	Email was received from FDA confirming they would be on the look out for the January 8, 2004 labeling amendment.
8-Jan-04	Labeling,Health Auth Comments Labeling	Labeling Amendment to revise and update the Patient Instructions for Use, cartons, foils and HandiHaler to be consistent with 30Dec03 version of the Package Insert which takes into account FDA's 23Dec03 comments.
13-Jan-04	Agency Contact Report	FDA telecon to discuss Clinical and Pharm/Tox and CMC issues between the BI Spiriva Team and management and FDA
14-Jan-04	Amendment to Unapproved NDA,Labeling	A labeling amendment for the package insert and the patient's instructions for use was made in accordance with the 13Jan04 tcon with FDA. This was a complete electronic submission.

14-Jan-04	Health Auth Comments CMC	FDA CMC Fax discussing cleanliness, hygiene, and defects of manufacturing, functional and assembly which are part of the HandiHaler specs provided in December 4, 2003 amendment and January 5, 2004 amendment. Request to modify wording.
15-Jan-04	Response to FDA Comments or Request for Information,Health Auth Comments CMC	Response to FDA Request for Information Fax 2004-01-14. Updated specification sheet Drug Product - degradant BIIS 56 SE to QC Testing Spec for DP and proposed a shelf-life accepance criterion of <0.5%
15-Jan-04	General Correspondence	Reference to January 13, 2004 telephone conference with FDA re clinical postapproval commitment and options to qualify selected degradation products.
15-Jan-04	Response to FDA Comments or Request for Information,Health Auth Comments CMC Field Copy	FIELD COPY to Complete Response to CMC IR of January 14, 2004 and CMC Commitment of January 13, 2004
15-Jan-04	Agency Contact Report	e-mails between BI and FDA regarding BI's commitment to clinical, toxicology, and CMC as discussed in 1/13/04 teleconference. Commitment attached to ACR and e-mails.
22-Jan-04	Response to FDA Comments or Request for Information,Health Auth Comments Clin PK	Response to FDA e-mail Jnauary 19, 2004 for all US and international SPIRIVA studies for which a report is completed
22-Jan-04	Health Auth Comments Labeling,Amendment to Unapproved NDA	BI submitted a labeling amendment in response to FDA's 22Jan04 email with labeling changes. The Package Insert and Patient's Instructions for Use were submitted in complete electronic format.
26-Jan-04	Amendment to Unapproved NDA,Labeling	Labeling Amendment - Patient Instruction and Package Insert
26-Jan-04	Agency Contact Report	ACR of FDA request for safety update tables from clinical trials referencing 282 deaths, unrelated to tiotropium bromide. Drs. Blank and Kaplan participated in discussion along with Peter Fernandes. Subsequent e-mail to Tony Zeccola along with table inc
30-Jan-04	FDA NDA Action Letter	FDA FAX - Spiriva Approval Letter
30-Jan-04	FDA NDA Action Letter	Official Approval Letter from FDA

EXHIBIT H

STATEMENT ASSERTING ELIGIBILITY OF U.S. PATENT 5,610,163 FOR EXTENSION

In the opinion of the Applicant, U.S. Patent No. 5,610,163 is eligible for extension under the provisions of 35 U.S.C §156.

(1) The term of this patent has not expired before this application is being submitted.

(2) The Term of this patent has never been extended.

(3) This application for patent term extension is submitted by an authorized agent of the record owner of the subject patent, Boehringer Ingelheim KG.

(4) The product has been subject to a regulatory review period before commercial marketing or use as evident from the information set forth in numbered paragraph 11 of the application for patent term extension.

(5) The permission for commercial marketing or use of the product after the regulatory review period is the first commercial marketing or use permission for the product under the provisions of Federal Food, Drug and Cosmetic Act.

(6) Applicant believes that the subject patent is entitled to **1,421 days** of extension.

The claimed extension has been calculated in the manner set forth in 37 C.F.R. §1.775.

Initially, the length of the regulatory review period was determined as set forth in 37 C.F.R. §1.775 (c). It is 3,284 days, which is the sum of:

(1) **2506 days,** the number of days in the period beginning on **2 February 1995**, the date the exemption under subsection (i) of section 505 of the Federal Food, Drug and Cosmetic Act for the approved product (IND No. 46, 687) become effective for the approved product and ending on **13 December 2001**, the date the application (NDA 21-395) was initially submitted for such product under section 505(b) of the Federal Food, Drug and Cosmetic Act; and

(2) **778 days**, the number of days in the period beginning on **13 December 2001**, the date the application (NDA 21-395) was initially submitted for the approved product under subsection (b) of section 505 and ending on **30 January 2004**, the date such application was approved under such section.

Next, the term of the patent as extended was determined in accordance with 37 C.F.R. §1.775 (d), by:

(1) subtracting from 3,284 **days**, the number of days calculated above to be in the regulatory review period, **1,253 days**, which is the sum of the periods set forth in 37 C.F.R. §1.775 (d)(1)(i), (ii) and (iii), as set forth in the following Table 1 below,

Table 1	
(i) the number of days in the periods of paragraphs (c)(1) and (c)(2) of 37 C.F.R. §1.775 which were on and before the date on which the patent issued	**0 days**
(ii) the number of days in the periods of paragraphs (c)(1) and (c)(2) of 37 C.F.R. §1.775 during which it is determined, under 35 U.S.C. 156(d)(2)(B) by the Secretary of Health and Human Services that the Applicant did not act with due diligence	**0 days**
(iii) one-half of the number of days remaining in the period defined by paragraph (c)(1) of 37 C.F.R. §1.775 after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) of 37 C.F.R. §1.775 (ignoring half days for the purposes of subtraction)	**1,253 days**

Which calculation yields **2,031 days** as its result;

(2) adding the number of days determined in accordance with 37 C.F.R. §1.775 (d)(1), **2,031 days**, to the original term of the patent as shortened by any terminal disclaimer (which term will expire on 11 March 2014), which calculation yields **2 October 2019** as it results;

(3) adding 14 years to **30 January 2004**, the date of the approval of the application under subsection (b) of section 505 of the Federal Food Drug and Cosmetic Act, which calculation yields **30 January 2018** as a result;

(4) comparing **2 October 2019** and **30 January 2018**, the dates for the end of the periods obtained pursuant to 37 C.F.R. §1.775 (d)(2) and (d)(3), respectively, with each other and selecting the earlier date, which comparison yields **30 January 2018** as its result; and

(5) **(as the original patent was issued after September 24, 1984)**

(i) by adding five (5) years to **11 March 2014**, the original expiration date of the patent or any earlier date set by terminal disclaimer, which calculation yields **11 March 2019** as its result; and

(ii) by comparing **30 January 2018** and **11 March 2019** the dates obtained pursuant to 37 C.F.R. §1.775 (d)(4) and (d)(5)(i) with each other and selecting the earlier date, which

comparison yields **30 January 2018** as its result (the new expiration date after extension).

The difference between 11 March 2014, the original expiration date of the patent, and 30 January 2018, the new expiration date of the patent, is **1421 days**.

EXHIBIT I

Application for Patent Term Extension
U. S. Patent No. 5,610,163

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re	:	U. S. Patent 5,610,163
Issued	:	March 11, 1997
Inventors	:	Banholzer, et al
For	:	Esters of Thienyl Carboxylic Acids And Amino Alcohols And Their Quaternization Products

Mail Stop Patent Extension
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

APPOINTMENT OF ATTORNEY FOR PURPOSES OF PATENT TERM EXTENSION UNDER 35 U.S.C. §156

Sir:

Boehringer Ingelheim KG, a corporation of the Federal Republic of Germany (hereinafter called "Boehringer"), is the assignee of the above-identified patent by virtue of an assignment from each of the inventors which was recorded on February 24, 1997, Reel 8368, Frame 0829.

Boehringer hereby appoints:

Robert P. Raymond, Reg. No. 25,089,
Michael P. Morris, Reg. No. 34,513,
Mary-Ellen M. Devlin, Reg. No. 27,928,
Alan R. Stempel, Reg. No. 28,991,
Timothy X. Witkowski, Reg. No. 40,232,
Anthony P. Bottino, Reg. No. 41,629,
Susan K. Pocchiari, Reg. No. 45,016,
Philip I. Datlow, Reg. No. 41,482 ,and
David A. Dow, Reg. No. 46,124.

as its attorneys to represent Boehringer in all matters before the United States Patent and Trademark Office as to an application for patent term extension as to U. S. Patent No. 5,610,163, to prosecute this application for patent term extension and to transact all business in the Patent and Trademark Office connected therewith, and request that all correspondence about the application be addressed to:

Robert P. Raymond
Boehringer Ingelheim Corporation
900 Ridgebury Road, P. O. Box 368
Ridgefield, CT 06877-0368

BOEHRINGER INGELHEIM KG
ppa.

By Dr. Heinz HAMMANN
Its
Hereunto Duly Authorized

Date

BOEHRINGER INGELHEIM KG
ppa.

By Dr. Heinz-Gerd KLÄS
Its
Hereunto Duly Authorized

Date